The Dynamic Interaction of Coronary Circulation, Left Ventricle and Aortic Valve during Exercise

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Abstract

Introduction

The left ventricle, aortic valve and coronary circulation are intimately related. In studying physiology and developing risk stratification models, these systems cannot be considered in isolation. The main aim of the thesis was to improve our understanding of the coupling mechanisms between left ventricle, aortic valve and coronary circulation during exercise in two patient populations: aortic stenosis and coronary microvascular disease.

Methods

To characterize the microcirculation and define the forces governing flow, patients with aortic stenosis, coronary microvascular disease and a control cohort underwent simultaneous intra-coronary pressure and Doppler flow assessment, at rest, during exercise and hyperemia.

In addition, patients with moderate to severe aortic stenosis, underwent exercise stress echocardiography and predictors of exercise capacity and the development of symptoms were examined.

Results

Despite a greater myocardial workload in AS patients compared to controls at rest and during exercise, coronary flow was similar. Hyperemic flow was less in AS compared to controls. At rest coronary flow was higher and microvascular resistance was lower in patients with micorvascular disease compared to controls.

With exercise and hyperemia, the relative contribution of accelerating waves increased in controls. The opposite pattern was seen in aortic stenosis and microvascular disease.

The cardiac output reserve, defined as the ratio of cardiac output on maximal exercise to the cardiac output at rest was the only independent predictor of exercise capacity in aortic stenosis and the best predictor of the development of symptoms on exercise.

Conclusions

Under conditions of stress, patients with aortic stenosis develop a mismatch between myocardial supply and demand. Both patients with aortic stenosis and microvascular disease have a pathophysiological reduction in coronary perfusion efficiency in response to exercise and hyperemia.

Cardiac output reserve is an objective measure that integrates the physiological contributions of valve, ventricle, systemic circulation and chronotropic competence and may proof a useful tool in the risk stratification in aortic stenosis.

Dedication

This thesis is dedicated first and foremost to my wife Thushyanthi; thank you for your unwavering belief, support and patience. Without you, I would not be where I am today, personally and professionally.

To my daughters, Aryanna and Sephina: you are my world.

Mum and Dad, thank you for always being there for me, I will always be in your debt. I hope I can do the same for my girls.

Shanthini and Nathan, thank you making me part of the family and treating me as if I were your own son.

Finally, I would also like to dedicate this thesis to Richard John Delmar Curtis, who tragically lost his life on 7th December 2014, a dear friend and someone who always showed great faith in me. Rest in Peace.

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The last few years have proven to be the most enjoyable of my career to date. This has been made possible by the support of many people, however several people deserve special mention.

My mentor and primary supervisor, Dr Divaka Perera, has been pivotal to the success of my research. Divaka's unrelenting drive and passion for research has served as an inspiration. Over the last 3 years he has always made the time to talk through problems big or small. These supervision meetings, both planned and impromptu, have provided some of the most enjoyable moments of this PhD. It is in these meetings, through intellectual discussion, I have been encouraged to think outside the box, develop a healthy skepticism of published data and explore my own thoughts and hypotheses. This process has been integral to my development towards becoming an independent investigator. Despite our careers now taking a divergent path, I am confident that we will work together in the future and remain friends. I have no doubt that Divaka will continue to climb the academic ladder inspiring many others like myself along his way.

To all the fellows, with whom I have worked closely over the last three years, we have shared some fantastic times and without you it would not have been possible to acquire this complex physiological data. I hope we all remain in touch.

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I owe a special debt to many clinical staff that have helped facilitate this study. Without your efforts, clinical research like this would not be feasible in our busy environment.

Finally to all the patients with cardiovascular disease who have participated in research. Without your altruistic acts, the phenomenal progress of medical science would not been possible.

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Chapter 1: Background

1.1 Overview of Aortic Stenosis

1.1.1 The Epidemic of Valvular Heart Disease

There has, and continues to be, a major shift in the aetiology of valvular heart disease, particularly in the developed world. This shift has been driven by the substantial decline in rheumatic disease and an ageing population meaning the now dominant aetiology of valvular disease is degenerative in nature[1][2]. Accurate estimates of the prevalence of valvular heart disease in the general population are difficult due to the silent nature of the disease and the requirement of echocardiography to establish the diagnosis. Previous attempts to estimate prevalence have also been biased by selecting hospital-based patients[3]. A recent population and community based study provides the best estimate of the prevalence of valvular heart disease in the US population[4]. The prevalence of echocardiographically determined moderate-severe left-sided valvular heart disease was estimated as 2.5%. Prevalence increases dramatically with age, with a prevalence of over 13% in those patients older than 75 years. Aortic stenosis (AS) was the second most prevalent valvular heart disease second to mitral regurgitation. It was present in over 1% of 65-74 years and over 4% of those aged greater than 75 years. It is clear that valvular heart disease, including AS represents a real public health burden that is likely to continue to increase.

1.1.2 Pathophysiology

AS, once thought to be a degenerative disease, is now understood to be an active process that has an inflammatory, fibrotic and finally a calcific stage [5][6][7]. As a result the term calcific aortic stenosis is preferred.

The normal aortic valve is made up of three cusps or leaflets (tricuspid valve). Each cusp is approximately 1mm thick and is made up of four distinct layers: the endothelium, fibrosa, spongiosa, and ventricularis. The base of each cusp is connected to the aortic valve annulus; a strong collagenous structure attached to the aortic root[7]. This arrangement theoretically allows near equal distribution of mechanical stress across the valve and aorta[8]. The reality is that there is considerable variation of valve leaflet size and anatomy and hence mechanical stress is not distributed uniformly[9]. The initiation of AS is due to endothelial damage triggered by high mechanical stress and low shear stress. It is the variable distribution of mechanical and shear stress that determines the location of the lesions of aortic stenosis. Shear stress is highest in cusps adjacent to the coronary ostia and lowest in the non-coronary cusp. As a result the non-coronary cusp is most commonly involved in AS. The importance of mechanical and shear stress in the pathophysiology of AS is highlighted in cases of bicuspid aortic valves where stenosis develops about two decades earlier than with tricuspid valves[10].

Endothelial damage caused by high mechanical and low shear stresses allows lipid to infiltrate the sub-endothelium. Oxidation of this lipid deposition in combination with endothelial damage drive the inflammatory response leading to release of pro-inflammatory and pro-fibrotic cytokines[11][12]. There is now ample evidence of the inflammatory component of AS; elevated levels of C-reactive protein have been demonstrated in patients, as well as increased temperature of stenosed aortic valves[13][14]. Disorganised thick fibrous tissue forms on the valve that leads to increased stiffness and reduced mobility. The differentiation of the myofibroblasts into osteoblasts drives the development of calcification. This calcification is pivotal

in the pathogenesis in AS. The degree of valve calcification is associated with valve stenosis severity[15], disease progression [16] and adverse events[17].

With increasing severity of AS and systemic arterial disease, the left ventricle must perform more work to overcome this dual resistance and maintain cardiac output. This necessitates higher left ventricular pressures and elevated wall stress. Wall stress as described by Laplace's law, is directly proportional to intra-cavity pressure and radius and inversely proportional to the thickness of the wall. Therefore the adaptive response of the ventricle is to hypertrophy, leading to increased wall thickness and reduced intra-cavity radius, which reduces wall stress. There is marked heterogeneity in the degree of hypertrophy which has only a minor association with the degree of valvular obstruction and seems to be more strongly correlated with age and sex[18][19][20][21]. Although hypertrophy has traditionally been felt to be adaptive, it may in fact be maladaptive leading to the pathological consequences of reduced ventricular compliance, increased myocardial oxygen demand, decreased coronary blood flow, eventual left ventricular systolic dysfunction and an increased rate of cardiovascular events[22][23][24].

Without surgical correction of the stenotic aortic valve the combination of high afterload state, progressive diastolic and systolic dysfunction leads to reduction in cardiac output and the subsequent syndrome of heart failure. One hypothesis of the trigger for progression from hypertrophy to left ventricular dysfunction is the process of myocardial apoptosis and replacement with myocardial fibrosis[25]. Myocardial fibrosis has been recognized in AS from histopathological studies[26] and more recently a correlation between ejection fraction (EF) and myocyte degeneration and fibrosis was demonstrated from surgical myomectomy samples taken at the time of

aortic valve replacement (AVR)[25]. In addition mid-wall fibrosis detected on cardiac MRI is an independent predictor of all cause mortality in patients with moderate to severe AS[27], is a predictor of improvement in New York Heart Association (NYHA) status and is associated with improvement in LVEF and all cause mortality following AVR[28][29]. Echocardiography using strain rate imaging can also non-invasively accurately identify regional myocardial fibrosis in AS[30]. The mechanism of increased mortality with increasing degrees of fibrosis may be due to increased ventricular stiffness[31], reduction in contractile function and hence systolic dysfunction[32] or fibrotic areas acting as a pro-arrhythmic substrate[33].

1.1.3 Therapeutic Targets in Aortic Stenosis

Currently no pharmacological treatment has been demonstrated to improve clinical outcomes in patients with aortic stenosis.

Inflammation and lipid deposition, which represent early triggering events in the disease process, have been the target of disease modifying therapies. To date three well conducted randomized control trials of statin therapy in AS have not shown a delay in disease progression or reduction in clinical endpoints[34][35][36]. It is possible that although inflammation and lipids represent a triggering event in the development of AS, it is osteoblast activation and valvular calcification that promulgate the disease and hence may represent better therapeutic targets[37]. Bisphosphonates have been shown to inhibit both vascular and valvular calcification,

however their effect on clinical endpoints in AS are yet to be tested in a randomized setting[38].

Patient symptoms and clinical endpoints are intimately related to the dynamic interaction of the left ventricle and aortic valve. The maladaptive ventricular response in AS therefore represents a logical therapeutic target. The use of angiotensin convertor enzyme inhibitors (ACE-I) in rodents with AS have been shown to reduce the decline in left ventricular systolic function and improve longevity[39][40][41]. Despite historical warnings of the use of vasodilating agents in patients with AS, ACE-Is appear not only to be well tolerated, but also may incur a survival advantage[42][43][44].

1.2 Coronary physiology

1.2.1 Setting the Scene

Angina pectoris has been reported in 30-40% of patients with symptomatic AS and normal coronary arteries however the precise mechanism is unclear[45]. Transthoracic Doppler echocardiographic studies have shown that coronary flow in AS is abnormal and characterised by early systolic flow reversal, delayed forward systolic flow and delayed peak diastolic flow[46]. Furthermore, coronary flow reserve (CFR) has been shown to be reduced in patients with aortic stenosis and normal coronary arteries[47].

Despite these observations being made over 30 years ago, the mechanisms of reduced CFR and abnormal coronary flow velocity patterns are poorly understood. A central theme of this thesis is an attempt to disentangle the dynamic interaction of the aortic

valve, left ventricle and coronary circulation in the development of symptoms, particularly angina in aortic stenosis.

1.2.2 Assessment of pressure and flow: Mean Indices

Cardiologists have long been interested in coronary blood flow. Until the advent of ultra-thin Doppler blood flow velocity sensors the measurement of coronary blood flow has been technically very difficult. Coronary flow is no longer routinely measured in the clinical assessment of atherosclerotic lesions but is a powerful tool in understanding the resistances of epicardial and microvascular compartments and also enables the study of phasic variations, as well as the effects of intervention on the magnitude and nature of flow.

The typical waveform of coronary flow velocity has a predominant diastolic peak. There is a rapid increase in diastolic flow velocity immediately after the dicrotic notch and a rapid fall off of the flow velocity after the onset of systole. There is usually a small systolic component of approximately 25% of the diastolic flow velocity at rest. The mean velocity can be calculated by the integrated area of flow during systole and diastole.

Coronary flow reserve (CFR) is a measure of the heart's ability to increase flow in response to demand. It is defined as the ratio of maximal coronary flow to basal coronary flow. Heart rate, mean arterial blood pressure, metabolic, vascular and endothelial factors affect CFR, which in turn affect reproducibility of this parameter. CFR can be impaired by stenosis of epicardial arteries and also microvascular dysfunction.

CFR has been shown to be reduced in patients with aortic stenosis and normal coronary arteries [47].

There is controversy over the normal value of CFR, which is likely due to the large number of factors affecting it and its lack of reproducibility, particularly microvascular disease.

Currently two invasive methods of assessing the coronary microcirculation exist: The index of microvascular resistance (IMR) and the hyperemic microvascular resistance(h-MR).

Prior to the development of the single wire pressure and flow velocity transducer Fearon et al[48] introduced the index of microvascular resistance (IMR). There is a strong inverse correlation between the mean transit time of saline injected down a coronary artery and the absolute flow. IMR is defined as distal coronary pressure divided by the inverse of mean transit time. By measuring IMR at maximal hyperaemia it gives a measure of minimum microvascular resistance. As both distal pressure and absolute flow fall in the presence of an upstream epicardial stenosis, IMR should be unaffected by epicardial stenosis (when the coronary wedge pressure is accounted for).

Hyperaemic Microvascular Resistance (h-MR) is the ratio of mean distal coronary pressure (P_d) to Average Peak Flow Velocity (APV) obtained from intracoronary pressure and Doppler sensors respectively during peak hyperaemia (h-MR = P_d/APV) [49][50].

To comprehensively analyse microvascular resistance more than the mean value of pressure and flow are required. Multiple measurements at different pressures should be made and a pressure-flow curve can be plotted. The gradient of this curve at any point represents the vascular conductance [51]. At physiological pressures these

curves are straight but at lower pressures become curvilinear towards the pressure axis. The curvilinear relationship is consistent with the pressure dependence of microvascular resistance. The point at which the curve intercepts the X-axis is the zero flow pressure (Pzf). This pressure is greater than the venous pressure suggesting that at lower pressures there is a reduced diameter or even collapse of the microvasculature[52].

The pressure flow line and Pzf are shifted to the right in left ventricular hypertrophy leading to a decrease in CFR[53].

Pressure flow curves have traditionally been taken during diastole or cardiac arrest. It can be shown that at a constant pressure during cardiac arrest there is increased flow as compared to the beating heart. This demonstrates that cardiac contraction impedes coronary perfusion [54]. This impedence is due to compression of intramural vessels during systole. The intramural compression is not uniform across the left ventricular wall, the highest pressure and greatest impedance is in the subendocardium. During systole compression of the subendocardium causes retrograde filling of the subepicardial vessels, as a consequence antegrade subendocardial filling occurs exclusively in diastole. With increasing heart rates and reduced diastolic time an increasing proportion of diastole is used to refill the subendocardium delaying the forward perfusion of the subendocardial microcirculation [51]. This dependence of subendocardial perfusion on diastolic time fraction (ratio of time in diastole to time for complete cardiac cycle) has been shown in anaesthetised goats using fluorescent microspheres to measure regional coronary flow[55].

1.2.3 Moving beyond means: Wave Intensity Analysis

The classical method of studying cardiovascular haemodynamics utilizes Fourier analysis. Fourier analysis describes the propagation of waves within the arteries in terms of periodic wavetrains formed by the superimposition of a mean value and sinusoidal waves at the fundamental frequency and its harmonics[56].

Fourier analysis has provided much information on arterial haemodynamics but is not without its drawbacks. The major drawback of frequency domain analysis is that it is difficult to relate to temporal events within the cardiac cycle to particular features in the frequency spectrum.

In 1990 Parker and Jones described a new approach to analysing haemodynamics, wave intensity analysis (WIA)[57]. The origins of WIA come from the study of gas dynamics during and after the Second World War[58]. WIA is based on the method of characteristics solution of 1-D equations derived from the conservation of mass and momentum within the elastic arteries. The underlying mathematics is complex but the results are extremely elegant allowing understanding and interpretation by non-mathematicians.

WIA depicts a waveform in terms of a succession of multiple small "wavefronts". These wavefronts can be described as the change in properties during a sampling period, Δt. Decreasing the sampling period leads to a more accurate analysis of the waveform.

From the solution of the method of characteristics it can be shown that any perturbations within an artery will propagate along the artery as a wave at speed U+c in the forward direction and U-c in the backward direction, where U is the velocity of

blood and c is the wave speed of the artery. It is important to appreciate that the wave speed is intrinsic to the elastic properties of the artery. The wave speed is a function of the pressure and the position in the arteries. For simplicity it can be assumed that the wave speed at any particular position is constant.

The wave intensity is defined as the product of the change in pressure and the change in velocity during a small interval (Δt). It is positive for forward waves and negative for backwards waves. Net wave intensity therefore describes whether at a particular time forward or backward waves are dominant.

When there is an increase in pressure, waves are termed compression waves and when there is a fall in pressure waves are termed expansion waves. Likewise when there is an increase in velocity waves are called acceleration waves and when there is a fall in velocity, they are termed deceleration waves.

The magnitude of wave intensity is dependent on the sampling interval (Δt). For different values of wave intensity to be compared they must be corrected for the sampling interval, the "time-normalized" WI.

If the wave speed is known it is possible to calculate the type and magnitude of waves at any given time.

Net wave intensity is determined by the sum of forward and backward waves that occur simultaneously. Therefore when net WI is small or zero, it does not mean that no waves are present, it is possible that large forward and backward waves are cancelling one another out. For this reason it is important to separate net WI into its forward and backward components, this is particularly important in the coronary circulation where backward waves are not just due to reflections but also distal forces such as external compression of the contracting myocardium.

As discussed above, wave speed is an intrinsic physical property of an artery and it varies from artery to artery and also at different positions along the same artery.

One way of expressing wave speed is given below.

$$c = 1/\sqrt{\rho D}$$

Where, c = wavespeed, ρ = density of fluid and D = distensibility of artery.

The wave speed is crucial to the separation of forward and backward waves but is an important property in its own right as changes in distensibility and hence wavespeed are linked to various physiological (ageing) and pathological (hypertension) states.

The calculation of wavespeed is difficult and has been the subject of much research. Accurate calculation of wavespeed remains an ongoing difficulty especially in vivo. It is particularly difficult within the coronary arteries, an area of vasculature where the separation of wave intensity into its forward and backwards components is principally important.

The currently used method for the calculation of wavespeed in the human coronary arteries is the single-point or sum of squares method[59]. This method of calculating wavespeed minimizes net wave energy over complete cardiac cycles.

$$c = \frac{1}{\rho}.\sqrt{\frac{\sum dp^2}{\sum du^2}}$$

In the validation studies, the wave speed in the aorta was compared to measurements made using the "foot-foot" method (a well established means of calculating wave-speed that is not possible in the coronary circulation) in fourteen subjects. They demonstrated good correlation between the two methods ($r=0.72$, $p<0.05$).

Davies et al[60] used WIA to analyse and separate the forward (ventricular) and backward (microcirculatory) contributions to coronary pressure and flow waveforms in twenty subjects with differing degrees of LVH. In each of the subjects a consistent pattern of six predominating waves was observed. Of the six waves, 94% of the energy accelerating blood distally along the coronary circulation came from two waves, the dominant forward compression wave and the dominant backward expansion wave.

The origin of the six identifiable waves can be explained physiologically. The early backward compression wave occurs early in systole before the opening of the aortic valve and is due to the compression of the intra-myocardial microcirculation. It causes increased pressure and deceleration (hence negative WI). The dominant forward compression wave occurs with ventricular ejection, it cause compression and acceleration of coronary flow. The final wave in ventricular systole is the late backward compression wave which is made up of two components: the reflected waves of the dominant forward compression wave; and ongoing compression of the coronary microcirculation by ventricular contraction.

There are also three recognizable waves seen during ventricular diastole. As the ventricle begins to relax the ventricular, aortic and coronary artery pressure falls. This causes the forward travelling expansion wave. As ventricular relaxation continues the microvascular resistance falls, as there is less compression by the contracting ventricle. This causes the dominant backward travelling expansion wave that continues until closure of the aortic valve. This briefly augments aortic pressure and leads to the late forward travelling compression wave and also acts to accelerate coronary flow (figure 1.1). WIA is unique in its ability to separate proximal and distal effects on arterial haemodynamics. This is particularly important within the

coronary vasculature. It may also prove to be fundamental to the understanding of the mechanism for syncope and angina seen in aortic stenosis in the presence of normal coronary arteries. Examining changes of WI during exercise in patients with AS is a unique experiment that has not been attempted previously.

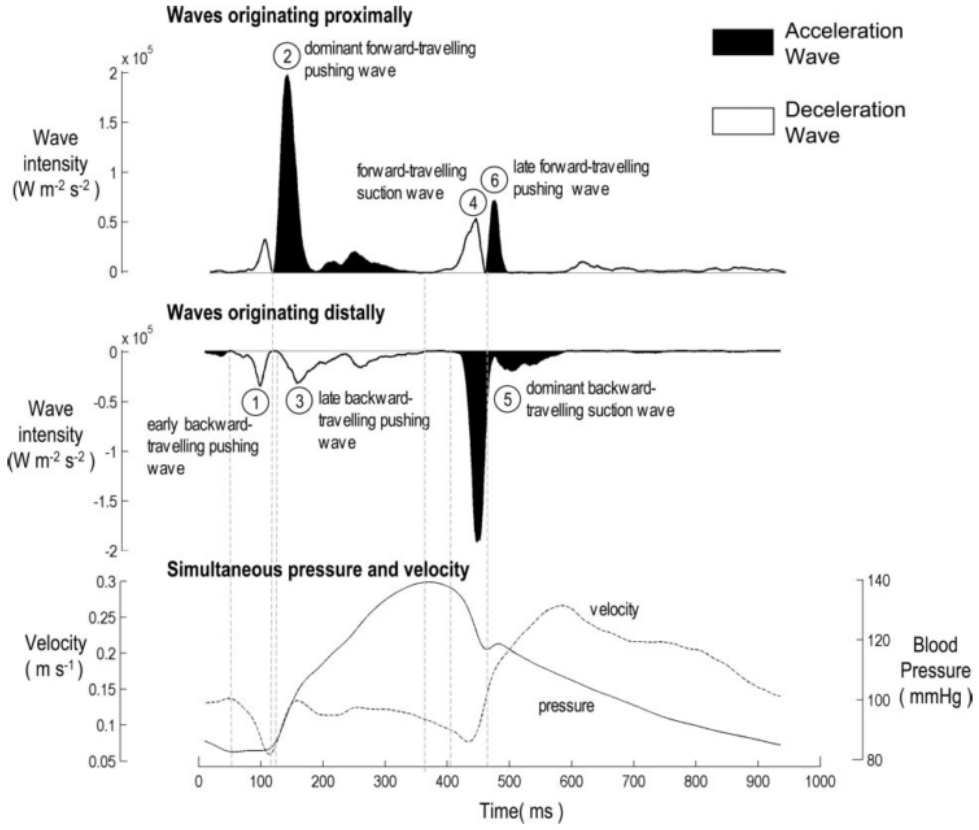

Figure 1.1: Coronary wave intensity profile. The 6 dominant waves during a single cardiac cycle are shown, with the relative phasic coronary pressure and velocity trends shown below the wave intensity analysis profile. Reproduced from [60].

1.2.4 Coronary Blood Flow during Exercise

During exercise, skeletal muscle requirements for oxygen increase. This increase in demand is met by local vasodilatation of resistance vessels and an increase in cardiac output. In providing this increase in cardiac output, there is an increase in each of the three major determinants of myocardial oxygen demand: heart rate, contractility and myocardial work.

Energy production in the normally functioning myocardium is primarily dependent on oxidative phosphorylation, with less than 5% ATP requirements coming from glycolytic metabolism. Because of this dependence on oxidative energy production and the continuous energy requirements of the contracting heart even in "resting conditions", myocardial oxygen extraction is 70-80%[61]. In times of increased oxygen demand (for example during exercise) myocardial oxygen extraction does increase however the principal mechanism of increased myocardial oxygen supply is augmentation of coronary blood flow[62][63][64][65][66].

The mechanisms that drive this augmentation in coronary blood flow are multifactorial and include neuro-hormonal mediated changes in both large and microvascular vessel tone and changes in mechanical forces on the coronary circulation[67].

The effect of the changing mechanical forces acting on the coronary circulation during exercise were studied by Duncker et al using a dog model[68]. Maximal coronary vasodilatation was maintained with an infusion of intravenous adenosine. Treadmill exercise led to a progressive increase in heart rate and fall in coronary blood flow despite increases in effective coronary perfusion pressure. The proportion of time spent in systole, cardiac contractility (leading to a greater degree of compression of the intra-myocardial vessels) and left ventricular diastolic filling

pressures all increase in response to exercise and all provide a mechanism for the reduced coronary flow observed in this study. Therefore one must conclude that the increases in coronary flow seen with exercise must be principally mediated by a fall in coronary vascular resistance.

1.2.5 Coronary Flow in Aortic Stenosis

Transthoracic Doppler echocardiographic studies have shown that coronary flow in AS is abnormal and characterised by early systolic flow reversal, delayed forward systolic flow and delayed peak diastolic flow[46]. Furthermore, coronary flow reserve (CFR) has been shown to be reduced in patients with aortic stenosis and normal coronary arteries[47]. CFR is also impaired in patients with aortic valve calcification before stenosis develops[69] and is an independent risk factor for future cardiovascular events[70]. One hypothesized mechanism of reduction of CFR is that it is secondary to microvascular dysfunction. Microvascular resistance is determined by both intrinsic properties of the resistance vessels (vascular resistance) and mechanical compression of the resistance vessels by the beating heart (extrinsic resistance). The intramyocardial arteriole thickening that is seen in LVH secondary to hypertension, is absent in AS[71] and microvascular dysfunction (and hence reduction in CFR) can be assumed to be secondary to external compressive forces. This hypothesis is supported by the findings of Rajappan et al[23] who found CFR reduced with increasing left ventricular rate pressure product (LVRPP), decreasing effective orifice area (EOA), diastolic perfusion time (DPT) and was independent of left ventricular mass (LVM). Further work by this group[72] has demonstrated that changes in microcirculatory function following aortic valve replacement (AVR) are

not directly dependent on regression of left ventricular mass, rather reduced extravascular compression and increased DPT are the proposed mechanisms of improved CFR following AVR. A three year follow-up study of patients following AVR for AS, demonstrated that CFR improvement was transient and CFR actually reduced at the end of follow-up[73]. This observation cannot be explained by extravascular compressive forces alone and therefore small vessel disease or progression of atherosclerosis must be responsible suggestive of intrinsic disease of the resistence vessels[73].

Reduction of CFR in AS is non-uniform across the myocardium and is more pronounced in the subendocardium[74]. Subendocardial perfusion is particularly sensitive to increasing heart rates as this leads to a progressive encroachment of systole on the diastolic interval and a reduction in DPT[51]. Ferero et al[75] demonstrated a close linear relationship between DPT at anginal threshold (during exercise or pacing induced tachycardia) and the degree of epicardial coronary stenosis. For a given degree of coronary stenosis the DPT at which symptoms developed was fixed and reproducible. Gould and Carabello[76] hypothesize that a similar relationship exists in AS; for differing severities of aortic valve stenosis, there may be a critical DPT at which symptoms of ischaemia will develop.

Angina and reduction in CFR in AS is likely related to an integration of the multiple negative influences on coronary perfusion. Elevated intra-cavity pressures will lead to increased subendocardial compression and a large pressure gradient across the aortic valve leads to a reduced coronary inlet pressure relative to intra-cavity pressure and hence a reduced pressure gradient driving flow. Systolic dysfunction will lead to a

reduction in forward flow and diastolic dysfunction will reduce the myocardial decompression effect that is the primary driving force for coronary perfusion. Additionally small vessel disease that may occur with myocardial remodeling will lead to elevated microvascular resistance. Hence it is easy to visualize why patients with AS can become rapidly ischaemic in the context of tachyarrhythmia or co-existent epicardial coronary artery disease.

1.3 Coronary Microvascular Disease

Calcific aortic stenosis is not the only condition that may present with evidence of myocardial ischaemia in the absence of obstructive coronary artery disease. In each of these conditions the coronary microcirculation is pivotal in the pathophysiology. Coronary microvascular dysfunction can be classified based on one of four clinical settings that it may occur: coronary microvascular dysfunction in the absence of obstructive coronary disease and myocardial diseases; coronary microvascular dysfunction in the presence of myocardial diseases; coronary microvascular dysfunction in presence of obstructive coronary artery disease and iatrogenic coronary microvascular dysfunction. It can also be classified based on the pathogenetic mechanism (table 1).

Alteration	Causes
Structural	
Luminal Obstruction	Microembolism in acute coronary syndrome or following recanalisation
Vascular-wall infiltration	Infiltrative heart disease (e.g., Anderson– Fabry cardiomyopathy)
Vascular remodelling	Hypertrophic cardiomyopathy, arterial hypertension
Vascular rarefaction	Aortic stenosis, arterial hypertension
Perivascular fibrosis	Aortic stenosis, arterial hypertension
Functional	
Endothelial dysfunction	Smoking, hyperlipidemia, diabetes
Dysfunction of smooth muscle cells	Hypertrophic cardiomyopathy, arterial hypertension
Autonomic dysfunction	Coronary recanalization
Extravascular	
Extramural compression	Aortic stenosis, hypertrophic cardiomyopathy, arterial hypertension
Reduction in diastolic perfusion time	Aortic stenosis

Table 1: Pathogenetic mechanisms coronary microvascular dysfunction. Reproduced from [77].

The underlying pathophysiology of microvascular dysfunction in the absence of obstructive or myocardial disease remains poorly understood. Some groups have demonstrated structural abnormalities, such as smooth muscle hypertrophy, of the small coronary arteries, whereas other have failed to demonstrate structural changes[78][79]. Functional changes have been demonstrated by a large number of authors, however the mechanisms of these functional changes are variable suggesting a heterogeneous pattern of disease. Impaired endothelial-dependent release of nitric oxide and subsequent impairment of vasodilation is the most commonly described functional abnormality, evidenced by a reduced coronary blood flow response to acetylcholine[80][81][82]. A reduced response to endothelium-independent vasodilators such as adenosine, as well as vasoconstriction in response to other stimuli, such as mental stress or exercise, suggests alternative functional mechanisms are at play[82][83][84][85].

Historically the long-term clinical outcome of patients with coronary microvascular dysfunction has been thought to be excellent, with similar rates of major cardiovascular events similar to the general population[86][87][88], however recent studies have contested this, demonstrating an unfavourable long-term prognosis[89].

1.4 Refining the assessment of Aortic Stenosis

1.4.1 Traditional grading of Aortic Stenosis

The cornerstone in the diagnosis of AS is transthoracic echocardiography (TTE). The classical measures used to diagnose and quantify AS are the peak flow velocity across the aortic valve (V_{max}), mean and peak pressure gradients across the AV (mean and peak AVG) and the effective orifice area (EOA) measured using the continuity equation. Each of these variables is easily measured however have significant limitations particularly when used in isolation. Both V_{max} and measures of AVG are highly flow dependent, over-estimate energy loss in patients with small aortas and underestimate AS severity in low-flow states. EOA is also flow dependent and prone to measurement error.

Despite extensive research into the pathophysiology it remains challenging to accurately predict the onset of symptoms in individual patients and hence appropriately plan surgical intervention.

Current guidelines[90][91] indicate surgery for patients with symptomatic severe aortic stenosis, or in patients with asymptomatic severe aortic stenosis with an ejection fraction (EF) <50% or a $V_{max} > 5ms^{-1}$. As such valvular intervention is driven by the presence or absence of symptoms in all but those with left ventricular dysfunction or those with very severe AS. However, these criteria are imperfect since: the risk of sudden death following the onset of symptoms nevertheless remains high; conventional echocardiographic measures of AS severity correlate poorly with symptoms[92]. Accordingly there is a need to refine current methods of assessing aortic stenosis. There is a growing body of evidence that to accurately assess the

severity of aortic stenosis, the contributions of the systemic circulation in addition to the degree of valve stenosis much be accounted for. Additionally LV remodeling is a heterogeneous process and should be quantified beyond resting LVEF to improve risk stratification.

1.4.2 Concept of combined after load

The left ventricular (LV) afterload, is the impedance or load against which, the left ventricle must work to promote forward flow and is an important determinant of cardiovascular function. In the presence of a normal aortic valve afterload is mainly regulated by properties of the arterial tree, namely the peripheral vascular resistance and the total arterial compliance.

Aortic pressure and flow waveforms are formed by the pulsatile interaction of left ventricle and systemic arterial load[93]. In the presence of aortic valve disease these waveforms are further influenced[94].

Both hypertension and AS represent different models of increased left ventricular afterload and both induce adaptive responses in the left ventricle in the form of left ventricular hypertrophy. Historically, in patients with aortic stenosis left ventricular afterload is considered to occur predominantly at the valvular level and is assessed using echocardiography through measurement of peak transvalvular pressure gradient, mean pressure gradient and effective orifice area (EOA). However there is increasing recognition that these conditions occur concurrently with hypertension being found in over 30% of patients with AS[95]. It is logical that these two pathological processes of increased afterload would have additive effects and a combined measure of LV

afterload may lead to better risk stratification in AS. The need for a combined measure of afterload is further justified as the presence of hypertension leads to lower measured EOA and transvalvular pressure gradients in AS[96]. Echocardiographic measures of AS are therefore not independent of downstream haemodynamic conditions and hypertension can therefore mask the severity of AS. This was demonstrated clinically by Antonini-Canterin et al[95] who performed Doppler echocardiography in 193 consecutive patients with symptomatic AS, 62 of which had a history of hypertension. In hypertensive patients, symptoms were present with larger aortic valve areas and lower stroke work loss.

Briand et al[97] were the first to propose a combined measure of left ventricular afterload. A total of 208 patients with moderate to severe AS were studied. The patients were divided into four groups based on AS severity and total arterial compliance (TAC). AS severity was determined by energy loss index (ELI), which is a pressure recovery adjusted measure of aortic valve area (AVA)[98][99][100]. TAC was estimated from the ratio of stroke volume index (SVi) to PP. In addition the valvulo-arterial impedance Z_{VA}, a global measure of combined LV afterload was proposed, formulated as follows

$$Z_{VA} = \frac{(SAP + MG_{net})}{SVi}$$

Where SAP is the systolic arterial pressure estimated measured non-invasively at the brachial artery, MG_{net} is the mean gradient pressure gradient accounting for pressure recovery and SVi the stroke volume index.

Patients with more severe AS and reduced TAC had a higher prevalence of LV diastolic and systolic dysfunction. Multivariate analysis revealed Z_{VA} to be only haemodynamic variable to be associated with LV dysfunction. Further studies into the role of Z_{VA} have shown that higher levels lead to LV systolic dysfunction in AS[101] and that Z_{VA} is an independent predictor of future clinical events in asymptomatic patients after adjustments for standard indices of stenosis severity[102]. A value of Z_{VA} >4.5mmHg.ml^{-1}.m^{-2} was associated with a 2.76 fold increase in the risk of overall mortality; whereas a value of Z_{VA} between 3.5 and 4.5 was associated with 2.30 increase in all cause mortality, providing compelling evidence that Z_{VA} should be incorporated into risk stratification models and clinical decision making in asymptomatic patients with AS.

1.4.3 Assessment of Left Ventricular Function in Aortic Stenosis

Myocardial fibres are predominantly orientated in a longitudinal axis within the subendocardium with a greater proportion of circumferential fibres within the midwall[103]. Wall stress and reduction in myocardial perfusion are most marked in the subendocardium. Therefore it would be logical to assume that longitudinal systolic function may in fact become impaired prior to global dysfunction. With the use of 2D speckle tracking echocardiography a progressive step-wise impairment of longitudinal, circumferential and radial strain and strain rate with increasing severities of AS severity has been shown despite preserved LVEF[104]. Other studies have also demonstrated impaired left ventricular longitudinal function in the presence of preserved LVEF and therefore LVEF, which is mainly a measure of LV radial systolic function is a relatively insensitive measure of systolic dysfunction in

AS[105][106][107]. Additionally longitudinal systolic dysfunction, measured by mitral ring displacement correlates with Z_{VA} and the degree of myocardial fibrosis and is a predictor of short term clinical outcome[28][108].

1.4.4 Rationale for studying AS during exercise

Under resting conditions the majority of patients maintain a normal cardiac output (CO) state. The most clinically relevant question is whether a patient is able to augment their cardiac output in response to stress and hence it is under these conditions that symptoms of angina and or dyspnea typically develop.
Moreover many patients underplay their symptoms and some are even unaware of their symptoms having made lifestyle adjustments over time as symptoms have progressed or even putting their limitations down to physiological ageing. Stress testing has a wide role in AS ranging from revealing unreported symptoms to unveiling pathophysiological mechanisms that cannot be examined during resting conditions. Although exercise has historically been regarded as dangerous in severe aortic stenosis, registry data has established its safety[109].

Rajani et al[110] performed exercise echocardiography in 38 apparently asymptomatic patients with moderate to severe AS. Of these, 10 patients developed symptoms on exercise. There was no difference in resting haemodynamic values between symptomatic and asymptomatic patients however B-type natriuretic peptide (BNP) levels were significantly greater in symptomatic patients. Symptomatic patients were unable to augment their CO to the same degree as asymptomatic patients with lower peak oxygen consumption (VO_2) and peak stroke index.

The prognostic significance of revealed symptoms on exercise was demonstrated by Das et al[111] who performed exercise tests on 125 apparently asymptomatic patients with an EOA < 1.4cm2. 37% of patients became symptomatic on exercise. All patients were followed for 12 months. In this time 29% reached the primary endpoint of development of exertional symptoms or sudden cardiovascular death. Of those patients who reached the primary endpoint, significantly more had limiting symptoms on exercise testing (72% vs 22%, $p<0.0001$). The positive predictive value and negative predictive value of limiting symptoms on exercise were 79% and 86% respectively (in a subgroup aged<70yrs and SAS class 1). These results are supported by studies from other groups[112][113].

Effective orifice area (EOA) has been shown to be dependent on cardiac output[114][115][116], therefore giving rise to the concept of AV compliance. The AV orifice area increases in area in response to a given change in pressure and hence non-compliant valves could further attenuate changes in CO in response to stress. Leurent at al[117] performed rest and semi-supine exercise Doppler echocardiography in 44 consecutive patients with aortic valve areas $<0.6 cm^2 m^{-2}$. 59% of patients had a positive exercise test according to ESC guidelines. There were no significant differences in baseline characteristics or Doppler echocardiographic measurements, at rest, between those with a positive and those with a negative EST. There was a significantly lower change in cardiac output, change in aortic valve area and change in stroke index, between patients with a positive, and those with a negative exercise test.

The findings of this study are supported by Das et al[118] who found that patients with a positive EST had a significantly reduced aortic valve compliance measured during dobutamine stress echocardiography.

The normal response to exercise of the systemic arterial tree is to reduce systemic vascular resistance (SVR) and TAC, however in AS further stiffening of the arterial tree has been observed[119]. To date, exercise capacity has not been shown to be dependent on arterial stiffness[120].

1.5 Improving Our Understanding of Aortic Stenosis

1.5.1 Why Is This Important?

Current international guidelines[121][122] and general consensus advocate delaying aortic valve replacement (AVR) until patients develop symptoms. Historically this management approach was without controversy as the annual risk of sudden cardiac death even with severe asymptomatic aortic stenosis is approximately 1% [123] and operative mortality was in the order of 3-4% [124][125]. Surgical techniques and aortic valve prostheses continue to progress and operative mortality is now approximately 1% in some high volume surgical centres [123] [17]. Given the comparable risk of sudden cardiac death with severe asymptomatic aortic stenosis and short-term surgical risk there is a strong argument to perform AVR in those high-risk asymptomatic patients. The limitations of traditional grading systems of aortic stenosis highlight the difficulties in accurately identifying those at highest-risk. Already much work as been done to improve the assessment of aortic stenosis, notably with the newer indices of global afterload such as Z_{VA}, use of exercise testing

and natriuretic peptides making it possible to better identify this higher risk cohort. Yet still there remains further scope to improve the risk stratification of AS. Newer indices such as Z_{VA} are particularly sensitive to changes in stroke volume index [126] and as such maybe further refined through dynamic assessment. Currently risk stratification is limited by the inability to integrate the contributions of aortic valve, left ventricle and systemic circulation into the risk stratification model of aortic stenosis. Changes in coronary physiology in AS, as well as its contribution to symptom development are poorly understood.

1.5.2 Aortic Stenosis: Drawing Parallels with Coronary artery Disease

Symptoms of aortic stenosis (AS) occur on exertion in all other than those with the most severe disease. This highlights that despite aortic valve stenosis, at rest there is adequate cardiac output to meet resting metabolic demands. It is only with rising oxygen demands that a mismatch develops. This is analogous to the presentation of stable coronary artery disease (CAD) where even in the presence of a severe coronary artery stenosis, anginal symptoms rarely manifest at rest and are classically exertional in nature.

The recognition of the manifestation of symptoms and signs of myocardial ischaemia under physiological stress has been integral to the assessment of coronary artery disease. For many years the exercise treadmill test (ETT) has been used to elicit symptoms and also electrocardiographic signs of myocardial ischaemia. Similarly dobutamine stress echocardiography (DSE) uses dobutamine as a pharmacological

stressor to look for changes in ventricular function that are indicative of myocardial ischaemia.

Just as ETT are used to assess patient symptoms in CAD, exercise testing can be used in AS to "reveal symptoms" in apparently asymptomatic patients with AS. This form of exercise testing although extremely useful remains subjective with respect to determining the presence or absence of symptoms.

When resting haemodynamic values are compared between truly asymptomatic patients and those with revealed symptoms on exercise no difference significant difference exists. Comparing haemodynamic indices at peak exercise the stroke volume index (SV_i), cardiac index (CI), cardiac power output (CPO) and oxygen consumption (VO_2) are lower in symptomatic patients as compared to asymptomatic patients[110]. This is analogous to CAD where resting coronary flow is maintained through vasodilatation of the coronary microcirculation thereby diminishing the ability of the coronary circulation to adapt to an increase in oxygen demand. In AS the stenosed valve necessitates higher left ventricular pressures and hence work to maintain stroke volume (SV) and cardiac output and also diminishing the ability to respond to demands under conditions of stress.

1.6 Aims and Objectives

The focus of this thesis is on the dynamic interaction between the intrinsically related left ventricle, aortic valve and coronary circulation. Two disease states, aortic stenosis and coronary microvascular disease, are studied. At rest differences in these

coupling mechanisms may not be apparent, therefore exercise is used as a stressor agent to unmask differences.

The mechanism of angina, reduced CFR and abnormal flow velocity profiles in aortic stenosis are poorly understood. We aimed to use the simultaneous measurements of intra-coronary pressure and flow at rest, during exercise and hyperemia to determine the relative contribution of vascular remodeling compared to changes in compressive microvascular resistance through altered cardiac-coronary coupling in the reduction in CFR in AS

Patients with coronary microvascular disease, by definition, have abnormal responses to different stressor agents (e.g. acetylcholine, adenosine). The presence of microvascular disease is associated with poor long-term outcomes. The aim of the study described in chapter 4 was to use different forms of stress, exercise and adenosine, to determine the possible underlying pathophysiology of coronary microvascular disease by examining the differing response to exercise and hyperemia. In addition, we aimed to use the modulation of the microvascular resistance through exercise and hyperemia to improve understanding of cardiac-coronary coupling and the efficiency of coronary perfusion.

Classical measures of aortic valve severity neglect the contribution of the left ventricle and system circulation, as a result they correlate poorly with the development of symptoms in AS. In addition they make no account of an individuals response to physiological stress. One aim of the thesis was to develop an index, analogous to CFR in coronary physiology, which would integrate the severity of valve

stenosis, left ventricular function and the afterload imposed by the systemic circulation. We hoped that this index could be shown to predict exercise capacity and the presence of revealed symptoms on exercise.

Chapter 2. Methods

2.1 Introduction

In this chapter the specific techniques used in this thesis will be outlined in detail. Three results chapters follow: the first describes a non-invasive echocardiographic study; the following two are invasive cardiac catheterization laboratory-based, coronary physiology studies. The techniques used in the latter two results chapters are very similar and differ only in inclusion and exclusion criteria of the enrolled patients. The identification and selection of patients for each study will be described in the corresponding results chapters.

2.2 Cardiac Catheter Laboratory Protocol

2.2.1 Cardiac catheter protocol overview

The principle aim of the invasive studies was to compare coronary physiology of different cohorts of patients (normal controls, severe aortic stenosis and microvascular disease) under resting conditions, during bicycle exercise and hyperaemia induced with the infusion of adenosine. In order to fulfill this aim, high-quality measurements of coronary pressure and flow velocity, followed by precise and reproducible analysis of these signals, was key to the success of the studies. The equipment used to acquire this high-fidelity data was the ComboWire and the ComboMap, both manufactured by Vocano Corporation (San Diego, California, USA).

2.2.2 Catheters and Medication

Patients were loaded with 300mg of aspirin and 600mg clopidogrel before the procedure. Angiography was performed via the right radial artery in all patients who performed supine bicycle exercise. In a minority of patients, all of whom did not complete the exercise protocol, the right femoral access route was used. All patients received 2mg of diazepam before local anaesthetic was administered and arterial puncture took place. Those patients who had radial access received 600µg-1mg of Isosorbide dinitrate into the radial artery before advancement of the diagnostic catheters. Prior to the acquisition of any research measurements, standard coronary angiographic views of left and right coronary arteries were acquired using standard diagnostic catheters. Intra-coronary isosorbide dinitrate was administered into the left and right coronary arteries before acquisition of the first diagnostic images (600µg-1mg). All research recordings were made via guiding catheters. In the large majority of cases 6F guides were used, however in some patients, typically small females with severe aortic stenosis, 5F catheters were used to minimize the risk of radial spasm.

2.2.3 Calibration and Optimization of Pressure and Flow Velocity Signals

The two pressure sources came from the ComboWire and a fluid-filled pressure transducer connected to the guide catheter. When exposed to ambient pressure, small differences in pressure readings exist. To correct for this, the fluid-filled pressure transducer was positioned to 0mmHg and the ComboWire pressure was zeroed. With the guide catheter in the aortic root, the tip of the ComboWire was advanced so it just protruded out of the guide catheter. At this point the two pressure signals were

compared. If the were any differences the ComboWire pressure was normalized to the fluid-filled catheter signal. Only when there was no difference between the two pressure signals was the guide engaged into the coronary artery ostium.

Drift of the pressure signal was occasionally encountered during the studies. When this occurred, the wire was exchanged and the study recommenced. Therefore no corrections were applied.

The ComboWire was then manipulated into the mid to distal coronary artery. Fine rotational movements were applied to the ComboWire to obtain the highest velocity readings. These readings occur when the Doppler probe is aligned co-axially with vessel wall (figure 2.1). This stage of the protocol is technically challenging and involves a learning curve for the cardiologist. With experience it is possible to recognize an optimal flow velocity signal from the shape of the envelope and the sound emitted from the ComboMap.

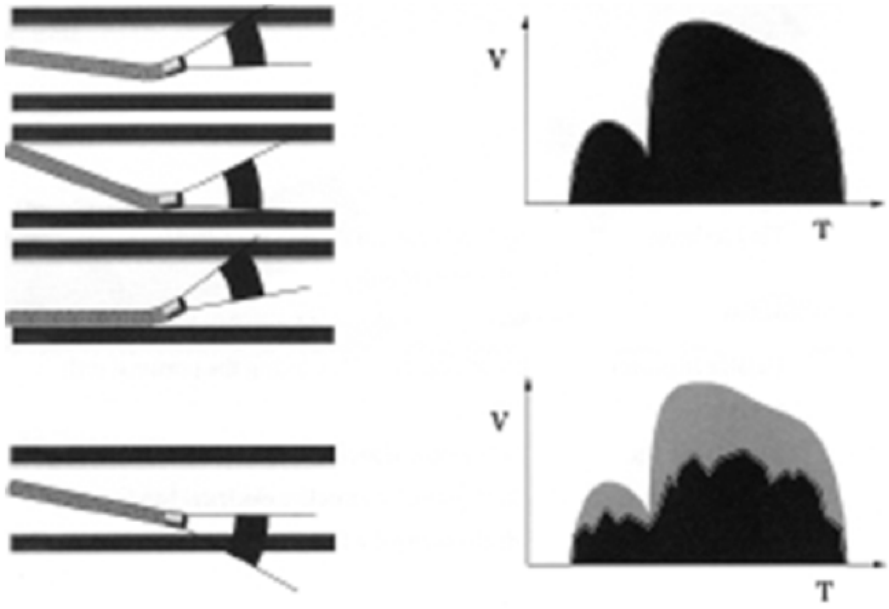

Figure 2.1: Mechanical Optimisation of the Doppler Flow Velocity Signal.

The flow velocity signal can be further optimized on the ComboMap machine. The IPV threshold is the signal to noise ratio and defines the threshold at which signals are considered as noise and therefore do not form part of the flow velocity measurements. This was optimized manually; as the threshold levels are changed it is possible to see how accurately the blue envelope tracked the velocity spectrum. It is important to use the minimum setting so not to filter out important physiological signals. By setting the IPV threshold too low, the quality of the envelope becomes corrupted by random noise. An IPV threshold set between 1 and 3 was used for all studies.

2.2.4 Physiological Conditions for Data Acquisition

Once an optimal Doppler velocity trace was obtained, the guiding catheter was then disengaged and haemodynamic measurements were taken under resting conditions and continuously during supine bicycle exercise

After the patient had made a full recovery from the exercise protocol (return to baseline levels of heart rate, blood pressure and average peak velocity), a second set of baseline haemodynamic data was acquired. This will be referred to as the Rest-2 period. Hyperaemia was then induced with intravenous adenosine. All relative changes that are reported with hyperemia (e.g. coronary flow reserve), use Rest-2 for baseline measurements.

2.2.5 Exercise Protocol and Induction of Hyperaemia

A specially adapted supine cycle ergometer (Ergosana, Germany) that allows a standardized incremental increase in workload was attached to the catheter laboratory table. Exercise began at a workload of 30 Watts and incrementally increased every 2 minutes by 20 Watts. Where muscle weakness restricted increasing workloads, the resistance was fixed at the maximum tolerated level and exercise continued until exhaustion.

Adenosine was administered peripherally via a central vein or large bore cannula into a large peripheral vein at a dose of $140 mcg.kg^{-1}.min^{-1}$. Hyperaemia was defined as the time of the steady state maximal average peak velocity.

2.3.6 ComboWire

The ComboWire XT is the only commercially available guide wire that is able to simultaneously measure pressure and flow velocity. The wire is 0.014" in diameter and is 185cm in working length (figure 2.2). It comes with two sensor-offset choices (0cm and 1.5cm). In the included studies the 0cm offset wire was used. This wire contains the pressure transducer and flow velocity sensor within a single housing at the tip of the guidewire. Before use the modular plug (for pressure) and the pin plug (for flow velocity) are connected to the pimmette of the ComboMap (model 6800).

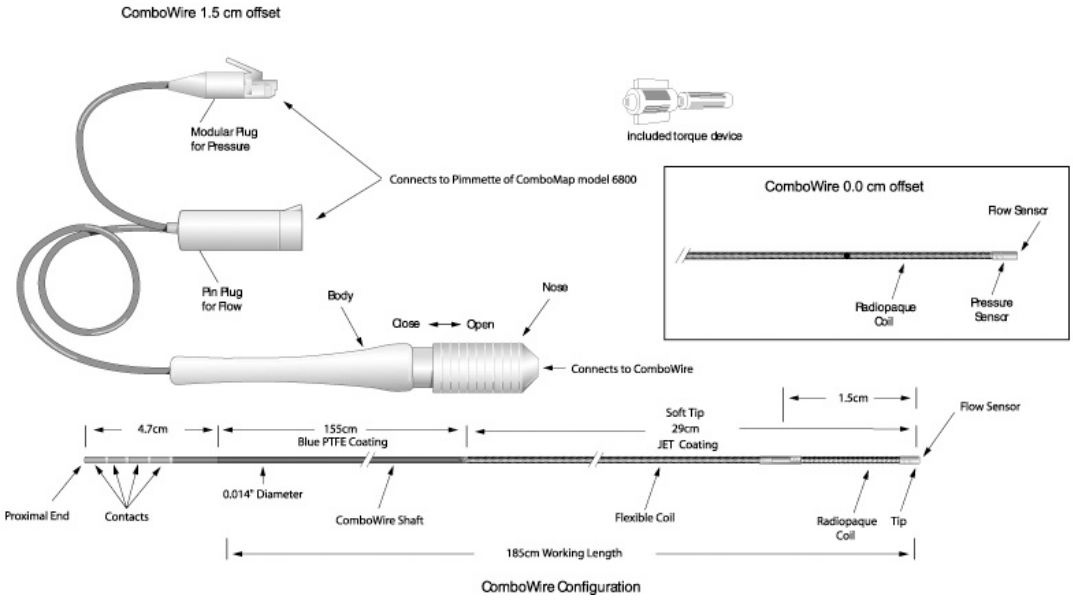

Figure 2.2: ComboWire XT technical drawing

2.3.7 ComboMap

The ComboMap console processes and displays the data acquired by the ComboMap. It has multiple ports that allow the processing of additional physiological signals. In our studies aortic pressure was slaved from the fluid–filled pressure transducer used

during coronary procedures. The patient's ECG was also inputted into the ComboMap. All inputted signals can be displayed simultaneously and scales can be adjusted (figure 2.3).

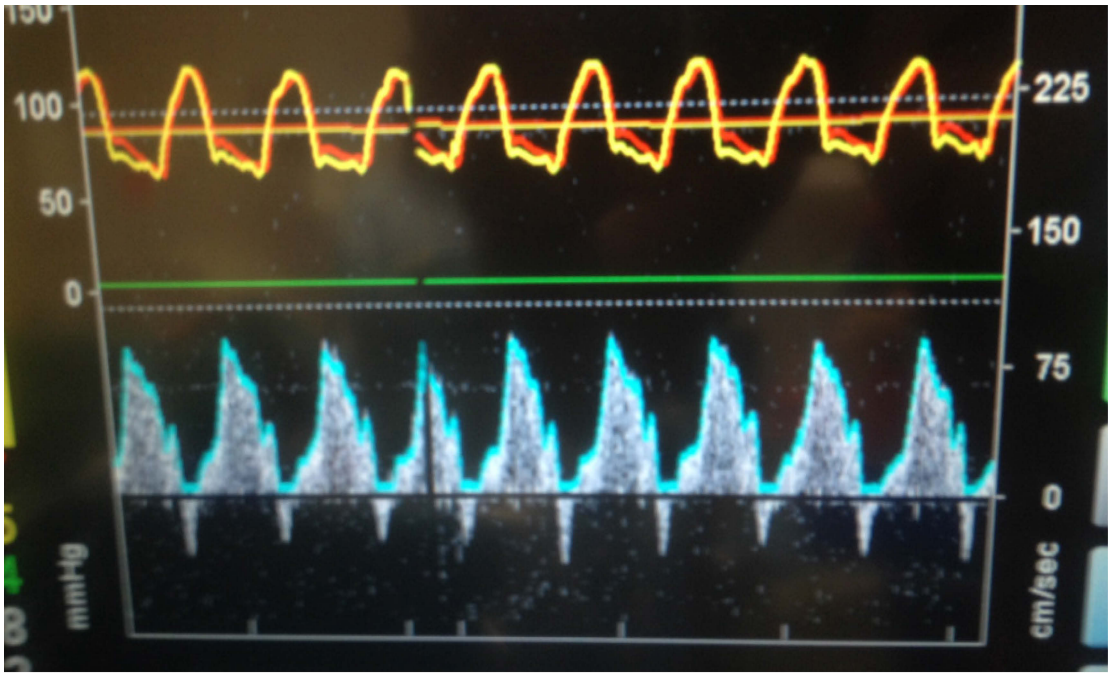

Figure 2.3: Screen display of on ComboMap Console. Picture taken from a patient with severe aortic stenosis. Yellow trace = distal coronary pressure (from the ComboWire); Red trace = aortic pressure (from fluid filled catheter); Grey-scale area = Doppler flow velocity signal; Blue Envelope = Instantaneous peak velocity envelope

2.3.8 Off-line Data Processing

At the end of the study procedure data was exported in the form of .SDY files. Study Manager was custom-made in collaboration between Volcano Corporation and the Academic Medical Centre, Amsterdam. The user can view all of the collected physiological variables (figure 2.4), select the cardiac cycles of interest (for example during maximal exercise) and convert the .SDY file in text file format for further analysis.

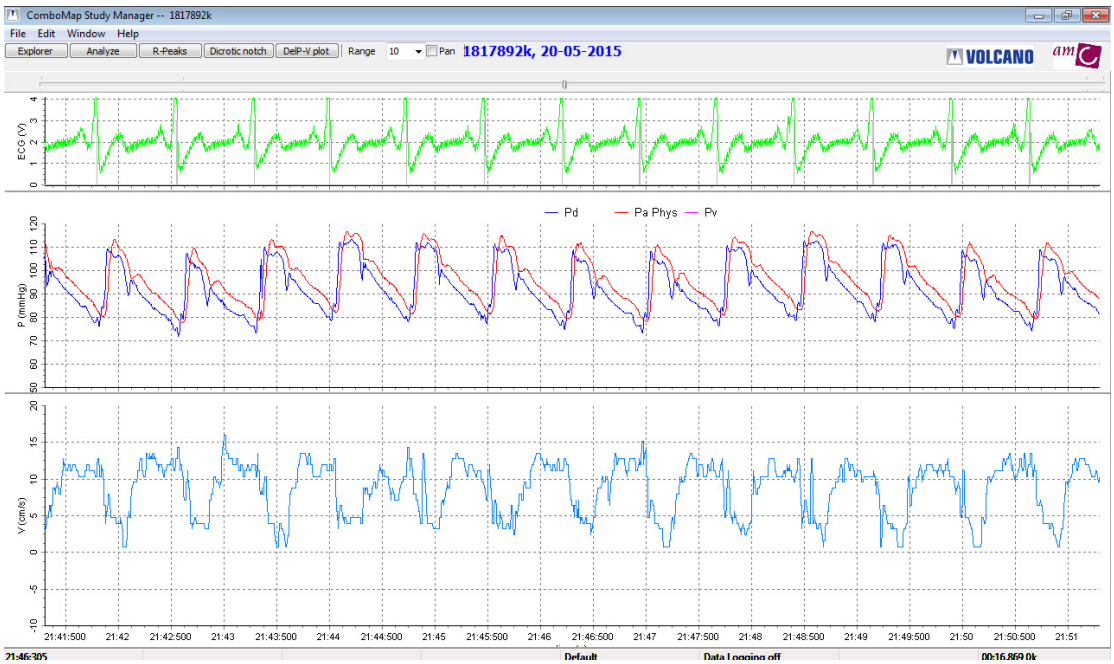

Figure 2.4: Screenshot of Study Manager Software

The exported text files were then analysed in CardiacWaves, a Matlab based application designed at Kings College London specifically for performing wave intensity analysis on invasive pressure and flow signals.

A minimum of 5, but typically at least 20 cardiac cycles were analysed in Cardiac Waves. The software allows the user to select which cardiac cycles to include and not include in the analysis. The flow and pressure signals were passed through Savitzky-Golay smoothing filters. They work by fitting a polynomial of a chosen order to a chosen number of points about the centre point using least squares. This has the advantage of preserving peaks in the data whilst smoothing [127]. The level of filtering can be directly controlled by changing the order of the polynomial and the frame width constants. All datasets included in the results was subjected to the same level of Savitzky-Golay filtering. The use of these filters represents a major breakthrough in the application of WIA to clinical data. Figure 2.5 is included to highlight the effectiveness of these filters; it shows two coronary WIA profiles using identical haemodynamic data, one with, and one without filtering.

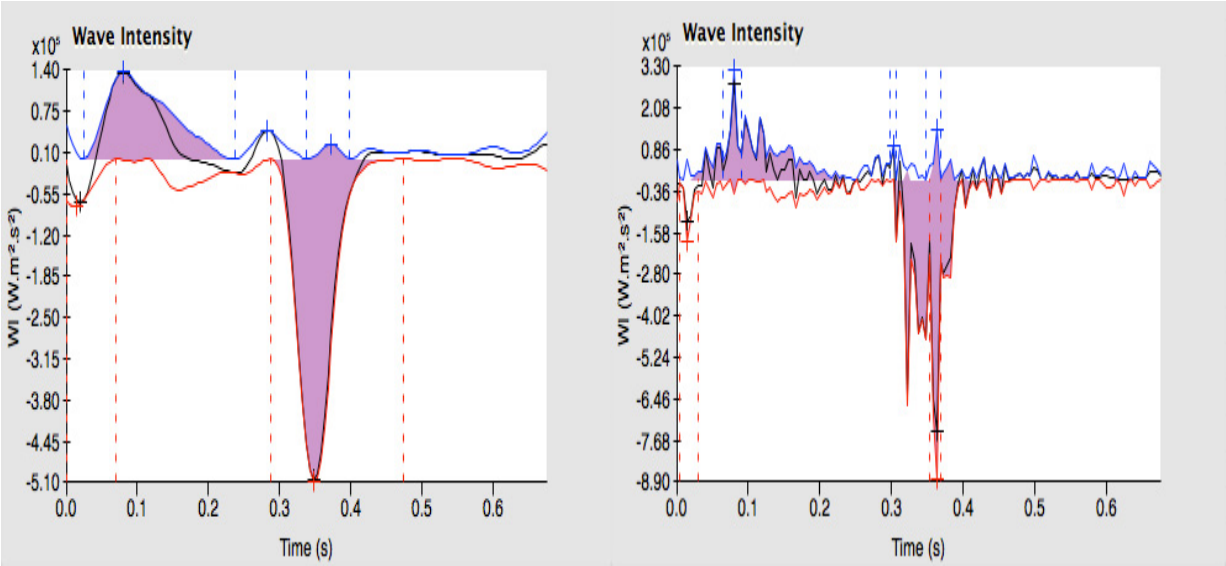

Figure 2.5: Coronary wave intensity analysis of identical haemodynamic data, with (left) and without (right) Savitzky-Golay filtering.

To perform wave intensity analysis, a single representative waveform is required. To do this an ensemble average of all the selected waveforms is produced. The software also has a quality control process in which each of the cardiac cycles can be superimposed on one another allowing outliers/non-physiological recordings to be quickly identified (figure 2.6). The process of ensemble averaging also has the advantage of filtering out background noise.

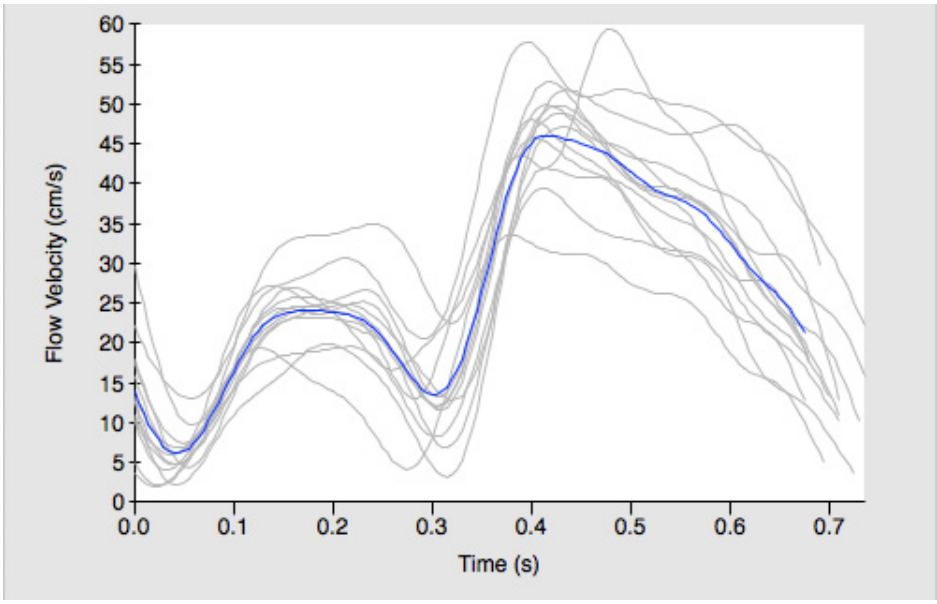

Figure 2.6: Ensemble average and quality control process of a coronary flow velocity signal. Each of the individual flow signals is shown in grey and the ensemble average of these flow signals in blue.

2.3.9 Pan-cardiac Cycle Indices

Microvascular resistance was calculated as the ratio of the distal mean coronary pressure, P_d and the average peak velocity, APV. The diastolic microvascular resistance (MR_{DIAS}) was defined as the microvascular resistance during mid to late

diastole where myocardial compressive forces are at their lowest[128]. Measuring MR in this interval gives insight into the vascular component of MR.

APV is affected by changes in heart rate or cardiac cycle duration and measurement assumes a constant shape in the velocity profile, an assumption that may not be valid during exercise[129][130]. The velocity time integral (VTI) overcomes many of these limitations and hence, we have used the product of VTI and HR (VTI.HR) to compare coronary flow between groups (control and AS) and conditions (rest, exercise and hyperemia).

2.3.10 Wave Intensity Analysis

Net wave intensity normalized for the sampling interval ($W.m^{-2}.s^{-2}$) was calculated from the time derivatives of the filtered and ensemble averaged coronary pressure and flow signals [58] (formula 2.1).

2.1 $$WI = \frac{dP_d}{dt} . \frac{dU}{dt}$$

Where dP_d and dU are incremental changes in measured coronary pressure and flow velocity between successive sampling intervals. When dP_d and dU change in the same direction the net wave intensity, WI is positive, and the wave is defined as forward travelling. It is also possible for dP_d and dU to change in opposite directions yielding a negative value for WI and the wave is defined as backward travelling. Waves are also defined by the change in pressure: if the wave corresponds to an increase in pressure, it is termed a compression wave; if the wave corresponds to a decrease in pressure, it is termed an expansion wave. Thus four types of waves are

possible: Forward compression wave (FCW); Forward expansion wave (FEW); Backward compression wave (BCW); Backward expansion wave (BEW)[131].

	Pressure	Flow	Net Wave Intensity
Forward Compression Wave (FCW)	↑	↑	Positive
Forward Expansion Wave (BEW)	↓	↓	Positive
Backward Compression Wave (BCW)	↑	↓	Negative
Backward Expansion Wave (BEW)	↓	↑	Negative

Table 2.1. The four types of wave defined by changes in pressure in flow at a point in the cardiac cycle

The net wave intensity itself is also made up of the contribution of forward and backward travelling waves arriving at the same measurement site (formula 2.2).

2.2 $$WI = WI_+ + WI_-$$

Where WI_+ represents the forward contribution and WI_- the backward contribution. It is possible the separate WI into the forward and backward components (formula 2.3).

2.3 $$WI_\pm = \pm \frac{1}{4\rho c}(dP \pm \rho c dU)^2$$

Where ρ = density of blood, c = wavespeed. This definition of separated wave has the problem of being dependent on the sampling interval. By doubling the sampling interval, the value of dP and dU are doubled and the magnitude of WI is increased.

dP and dU can be normalized for the sampling interval, thus overcoming this problem (formula 2.4)

2.4 $$WI_{\pm} = \pm \frac{1}{4\rho c}(\frac{dP}{dt} \pm \rho c \frac{dU}{dt})^2$$

It can be seen that separation of net wave intensity into its forward and backward components is only possible if the wavespeed is known.

Locally induced changes in pressure and flow are not transmitted instantaneously through the arterial wall, but propagate as waves at a certain speed, known as the wavespeed [132]. Wavespeed is inversely dependent on vessel wall distensibility (formula 2.5)

2.5 $$c = 1/\sqrt{\rho D}$$

Where D = vessel wall distensibility.

In addition to being an important parameter for WIA, wavespeed is an important physiological parameter in its own right as it provides information on the vessel wall properties[133]. Wavespeed was calculated using the single-point technique[59].

2.3.11 Estimation of Rate Pressure Product in Aortic Stenosis

A subset of patients with aortic stenosis were randomly chosen to undergo bicycle stress echocardiography so that the rate pressure product could be estimated (n=13).

All patients had a full resting transthoracic echocardiographic study followed by a bicycle stress echocardiogram. The exercise protocol used during the stress echocardiogram was identical to the protocol used in the catheterization laboratory.

Stress echocardiographic measurements were used to quantify myocardial work in AS patients, defined as the rate pressure product (RPP) or the product of heart rate and left ventricular systolic blood pressure, which has been shown to correlate with myocardial oxygen consumption[134]. Left ventricular pressure was estimated from the sum of systolic blood pressure SBP and the transvalvular pressure gradient after pressure recovery (MG_{NET})[135]. In the control cohort, left ventricular pressure was assumed to be equal to aortic pressure in systole and hence the RPP was calculated as the product of heart rate and aortic systolic pressure.

2.3 Echocardiography laboratory protocol methods

2.3.1 Brain Natriuretic Peptide Measurement

B-type natriuretic peptide was measured using the point-of-care Alere Triage BNP assay (Biosite diagnostics, California, USA). This assay is a rapid, point of care fluorescence immunoassay used with the Alere Triage® MeterPro. Blood was collected by venepunture into 4.5ml tubes anticoagulated with EDTA. All measurements were taken prior to either of the exercise protocols and following a 5-minute period of rest.

2.3.2 Transthoracic Echocardiography

All transthoracic echocardiograms were performed using a GE Vivid 7 dimension system (GE Medical Systems, Milwaukee, WI, USA) according to standard protocols [136]. The sub-aortic diameter was measured on parasternal long-axis frames frozen in systole taking an average of three estimates from inner edge to inner edge 5-10mm below the base of the cusps. Pulsed Doppler recordings were made in the apical five-chamber view just apical to the aortic valve. Continuous-wave recordings were made from the apex and right intercostal positions. Optimal signals were traced to obtain peak velocity, mean pressure difference, velocity-time integral. The systolic ejection time was measured from the continuous-wave Doppler recording as the time from the onset of systolic flow to its cessation. The EOA in square centimeters was calculated by the classical continuity equation using the ratio of sub-aortic to trans-aortic velocity integrals. For all Doppler measurements, the average of three signals was taken. Pulsed tissue Doppler signals were recorded from the apical four-chamber view. Peak systolic velocity (S') was measured at the lateral mitral valve annulus. Tissue Doppler imaging was also used to determine the early diastolic velocity (E'). The ratio of peak transmitral E velocity to Doppler tissue E' velocity (E/E') was calculated[137]. For all patients the energy loss index (ELI)[138] was calculated to account for pressure recovery distal to the aortic valve (Formula 2.6). The combined LV outflow (Z_{VA}) impedence was estimated (Formula 2.7).

2.6. $$EOA = \left[\frac{(EOA * Aortic\ Area)}{(Aortic\ Area - EOA)}\right] / BSA$$

2.7 $$Z_{VA} = \frac{Systolic\ Blood\ Pressure + MG_{NET}}{SVI}$$

BSA = body surface area; MG_{NET} = mean aortic valve gradient after post-stenotic pressure recovery; SVI = Stroke Volume Index.

2.3.3 Exercise Treadmill Testing

Exercise testing (ETT) was performed with a Marquette Case 8000 system (GE Medical Systems, Milwaukee, WI, USA) according to American College of Cardiology and American Heart Association practice guidelines [139] using a Bruce protocol modified by two warm-up stages[140]. Heart rate, blood pressure, and a 12-lead electrocardiogram was recorded at each stage of exercise. A physician and a cardiac physiologist supervised all tests. Subjects were asked about symptoms every 2 minutes and the test was stopped prematurely in the event of limiting breathlessness, chest discomfort, or dizziness. It was also stopped for, ST- segment depression > 5 mm measured 80ms after the J point, more than three consecutive ventricular premature beats or a decrease in systolic blood pressure of >20 mmHg from baseline. There was a cool down period of 1 minute at a slow treadmill speed. The heart rate reserve (HRR) was defined as the percentage increase heart rate from rest to maximal exercise.

The exercise capacity (EC) was defined as the time from the treadmill being started to the start of the cool down period. Exercise time on the treadmill was chosen to define exercise capacity as untrained athletes usually terminate cycle exercise because of quadriceps fatigue, with an oxygen consumption on average 10-20% below their oxygen consumption during treadmill exercise[141][142].

2.3.4 Bicycle stress echocardiography

Following the resting transthoracic echocardiogram, all patients underwent a bicycle stress echocardiogram. This was performed on a purpose designed supine bicycle (Ergosana, Germany), which could be tilted to optimize image acquisition. Exercise began at a workload of 30 Watts and incrementally increased every 2 minutes by 20 Watts. Where muscle weakness restricted increasing workloads, the resistance was fixed at the maximum tolerated level and exercise continued until exhaustion. At each stage of exercise the 4-chamber; 5-chamber, 2-chamber; 3-chamber and parasternal long and short images and LVOT and AV VTI Doppler recordings were acquired.

In order to account for the baseline variability in resting stroke volume, we calculated the relative change in stroke volume (Stroke Volume Reserve, SVR) and the relative change in cardiac output (Cardiac Output Reserve, COR), both expressed as percentages.

SVR was calculated as the percentage increase in stroke volume during exercise from the resting value of stroke volume (formula 2.8).

2.8. $$SVR = \left[100\left(\frac{SV_{EX}}{SV}\right)\right] - 100$$

Where SV_{EX} is the stroke volume during maximal bicycle exercise and SV is the resting stroke volume.

COR was calculated as the percentage increase in cardiac output during exercise from the resting value of cardiac output (formula 2.9).

2.9. $$COR = \left[100\left(\frac{CO_{EX}}{CO}\right)\right] - 100$$

Where CO_{EX} is the cardiac output during maximal bicycle exercise and CO is the resting cardiac output.

2.3.5 Referral for Surgery

The decision to refer for surgery was made by the specialist valve team, who had access to the results of the resting and exercise echocardiogram, treadmill test and BNP result, but not derived functions such as Z_{VA} and COR. All patients with symptoms (volunteered or revealed) were referred for surgery, as per the current guidelines.[122]

Chapter 3: Coronary Physiology of Aortic Stenosis During Stress: An Imbalance of Forces

3.1 Abstract

Background

Severe aortic stenosis (AS) with unobstructed coronary arteries is associated with exertional angina and an increased incidence of perioperative myocardial infarction. Precise mechanisms have yet to be elucidated.

Methods and Results

Simultaneous intracoronary pressure and flow velocity recordings were made in the unobstructed coronary arteries of 22 patients with severe AS (mean effective orifice area 0.7 cm^2) and 38 controls, at rest, supine bicycle exercise and during hyperemia. Stress echocardiography was performed to estimate myocardial work. Wave intensity analysis was used to quantify waves that accelerate and decelerate coronary flow. Despite a greater myocardial workload in AS patients compared to controls at rest (12721 vs. 9707mmHg.min^{-1}, p = 0.003) and during exercise (27467 vs. 20841mmHg.min^{-1}, p = 0.02), coronary flow was similar in both groups. Hyperemic flow was less in AS compared to control (2170 vs. 2716cm.min^{-1}, p = 0.05). With exercise and hyperemia, the relative contribution of accelerating waves increased in controls. The opposite pattern was seen in AS, driven by an augmented rise in the decelerating backward compression wave and an attenuated rise in the accelerating forward compression wave.

Conclusion

Under conditions of stress patients with AS develop a mismatch between myocardial supply and demand, governed by an imbalance of forces that drive coronary flow. This pathophysiological response provides a mechanism for reduced coronary flow reserve, which may explain anginal symptoms.

3.2 Introduction

Patients with symptomatic severe aortic stenosis commonly experience exertional angina and are also at an increased risk of myocardial infarction when undergoing non-cardiac surgery[143], even in the absence of obstructive coronary disease. The explanations for of both these phenomena are likely to be related to an inability to augment blood flow in response to stress, however the precise mechanism remains elusive[45].

Coronary flow reserve (CFR) has been shown to be reduced in patients with aortic stenosis and normal coronary arteries[47]; additionally abnormal coronary flow velocity profiles are well documented[46]. However these observations give little insight into the forces attenuating flow augmentation. The reduction in CFR may be related to increased baseline flow or diminished flow on stress, which in turn could be due to changes in microvascular resistance, secondary to cardiac remodeling or altered cardiac-coronary coupling mechanism secondary to the stenotic valve. The findings of Rajappan et al[23] support the hypothesis that reduced CFR is predominantly related to alterations in cardiac-coronary coupling. The reduction in CFR was found to be proportional to left ventricular rate pressure product (LVRPP) and inversely proportional to effective orifice area (EOA) and diastolic perfusion time (DPT) but was independent of left ventricular mass (LVM).

The traditional invasive study of coronary physiology has involved the measurement of coronary flow velocities and pressures that are averaged over several cardiac cycles. Although informative, these pan-cardiac cycle measures neglect the phasic

components of the recorded signals and therefore obscure any mechanistic insight into the forces promoting and attenuating coronary flow. The technique of wave intensity analysis (WIA), utilizes simultaneous changes in coronary pressure and flow to define the origin and magnitude of the forces driving and impeding coronary flow, at each point of the cardiac cycle.

Thus far, coronary WIA in AS has only been determined in patients during general anaesthesia undergoing trans-catheter aortic valve insertion (TAVI), with and without pacing [144], when hemodynamic conditions are non-physiological. The aim of our study was to compare the forces that govern coronary flow, at rest, during maximal exercise and during hyperemia in patients with severe symptomatic aortic stenosis and normal controls.

3.3 Methods

A detailed description of the cardiac catheterization protocol, haemodynamic analysis and exercise protocol can be found in the methods chapter (chapter 2). Only the patient selection and statistical methods are described below.

3.3.1 Patient Selection

Aortic stenosis and control patients were recruited from routine waiting lists for coronary angiography. The first group had severe symptomatic aortic stenosis (defined as EOA < $1cm^2$ or V_{max} > $4ms^{-1}$) under consideration for surgical aortic valve replacement (AVR). The second group (control cohort) comprised patients without AS awaiting coronary angiography for investigation of chest pain symptoms. Inclusion criteria were preserved left ventricular function (left ventricular ejection fraction > 50%) and unobstructed coronary arteries (no lesion > 50% in diameter assessed visually). Exclusion criteria were concomitant valve disease (> mild on echocardiography), history of syncope, recent acute coronary syndrome or presentation with heart failure (within 4 weeks) or any comorbidity that may influence exercise tolerance. The study protocol was approved by the institutional research ethics committee (NHS REC reference: 12/LO/1787). All of the participants were provided with an information sheet detailing the study protocol before obtaining informed consent.

3.3.2 Statistical Methods

Statistical analysis was performed using IBM SPSS version 21. Normality of data was visually assessed (using histograms and the normal Q-Q plot) and formally tested, using the Shapiro-Wilk test. Continuous and normal data are expressed as mean ± SD and compared using paired or unpaired t-tests as appropriate. Non-normal continuous data are expressed as median with interquartile range and compared using Mann-Whitney U test or Wilcoxon signed-rank test as appropriate. A 2-tailed test for significance was performed in all of the analyses; $P \leq 0.05$ was considered statistically significant. Correlation was assessed with the Pearson correlation coefficient. The authors had full access to and take full responsibility for the integrity of the data.

3.4 Results

3.4.1 Study Population

Sixty patients were recruited into the study: 22 had aortic stenosis and 38 comprised the control group. Table 3.1 displays the baseline demographics of the enrolled patients. The AS cohort all had severe symptomatic AS with a mean effective orifice area (EOA) of 0.7 cm^2 and a mean peak aortic valve gradient (pAVG) of 92mmHg.

All 22 AS patients and 17 consecutive patients in the control group performed supine bicycle exercise. Hyperemia was induced in 19 patients in the AS group and 30 in the control group.

	Control	**Aortic Stenosis**	**P-value**
Age, mean ± SD	61 ± 10	69 ± 8	0.001
Hypertension, n %	22 (58)	11 (50)	0.55
Diabetes Mellitus, n %	8 (21)	3 (14)	0.47
Hypercholesterolaemia, n %	27 (71)	14 (64)	0.55
Smokers, n (%)	7 (18)	2 (9)	0.33

Table 3.1: Patient Demographics by group

3.4.2 Pan-Cardiac Cycle Hemodynamic Data

Hemodynamic parameters in both groups are shown in table 3.2. At rest, diastolic microvascular resistance was lower in AS patients than controls (354 ± 172 versus 480 ± 220, p=0.025) and diastolic time fraction was lower in AS patients. In response to exercise, the heart rate and systolic blood pressure increased and the diastolic time fraction decreased in controls as well as AS patients ($p < 0.001$ in both groups). Coronary flow (VTI.HR) increased and microvascular resistance (both pan-cardiac cycle MR and MR_{DIAS}) fell during exercise in both groups ($p < 0.001$).

The induction of hyperemia led to a rise in heart rate but a fall in systolic blood pressure in both groups ($p < 0.001$). Diastolic time fraction decreased in controls ($p = 0.006$) but not in AS ($p = 0.1$). Coronary flow increased ($p < 0.001$) and microvascular resistance fell with hyperemia in both groups ($p < 0.001$).

Exercise CFR in the control and AS groups was similar (1.7 ± 0.6 vs. 1.7 ± 0.6 respectively, $p = 0.57$) but hyperemic CFR was greater in controls than AS patients (2.5 ± 0.6 vs. 1.9 ± 0.7 respectively, $p = 0.006$). The relative change in microvascular resistance between controls and patients with AS on exercise was not different (0.8 ± 0.3 vs. 0.8 ± 0.3, $p = 0.70$; the closer the value is to 1, the smaller the reduction from baseline), however this relative change was greater in controls compared to AS during hyperemia (0.4 ± 0.1 vs. 0.6 ± 0.3, $p = 0.001$).

	Rest			Maximal Exercise			Hyperaemia		
	Control	**Aortic Stenosis**	**P-value**	**Control**	**Aortic Stenosis**	**P-value**	**Control**	**Aortic Stenosis**	**P-value**
Number of patients, n	**38**	**22**		**17**	**22**		**30**	**19**	
				Aortic Haemodynamics					
HR, bpm	**73 ± 15**	**75 ± 16**	**0.67**	**124 ± 32****	**117 ± 25****	**0.46**	**83 ± 22****	**90 ± 16****	**0.24**
SBP, mmHg (invasive)	**131 ± 27**	**130 ± 19**	**0.85**	**165 ± 33****	**155 ± 27****	**0.33**	**125 ± 23****	**123 ± 18****	**0.74**
DBP, mmHg	**80 ±11**	**68 ± 11**	**0.02**	**86 ± 15**	**80 ± 12****	**0.19**	**70 ± 13****	**66 ± 11**	**0.19**
AI, %	**41 ± 27**	**66 ± 24**	**0.001**	**18 ± 24***	**59 ± 18**	**< 0.001**	**33 ± 32**	**59 ± 24**	**0.004**
DTF	**0.58 ± 0.07**	**0.53 ± 0.09**	**0.016**	**0.45 ± 0.11****	**0.40 ± 0.08****	**0.11**	**0.54 ± 0.07****	**0.50 ± 0.08**	**0.05**
RPP, bpm.mmHg	**9707 ± 2925**			**20841 ± 7622****					
				Coronary Haemodynamics					
APV, cm^{-1}	**18 ± 5**	**19 ± 8**	**0.45**	**26 ± 11****	**30 ± 10****	**0.29**	**45 ± 16****	**36 ± 15****	**0.05**
VTI, cm	**15 ± 5**	**15 ± 7**	**0.72**	**13 ± 5**	**15 ± 4**	**0.13**	**35 ± 16****	**25 ± 15****	**0.013**
VTI.HR, $cm.min^{-1}$	**1052 ± 327**	**1130 ± 476**	**0.45**	**1577 ± 653****	**1794 ± 599****	**0.29**	**2716 ± 952****	**2170 ± 886****	**0.05**
MR, $mmHg.cm^{-1}.s^{-1}$	**631 ± 244**	**547 ± 238**	**0.2**	**520 ± 200****	**409 ± 195****	**0.09**	**229 ± 104****	**282 ± 144****	**0.14**
MR_{DIAS}, $mmHg.cm^{-1}.s$	**480 ± 220**	**354 ± 172**	**0.025**	**334 ± 153****	**225 ± 125****	**0.02**	**154 ± 73****	**168 ± 93****	**0.55**
P_d/P_a	**1.00 ± 0.12**	**0.93 ± 0.07**	**0.05**	**0.98 ± 0.11****	**0.93 ± 0.06****	**0.06**	**0.97 ± 0.13****	**0.93 ± 0.07****	**0.22**

*Table 3.2: Pan-cardiac cycle haemodynamics and stress echocardiography data. Values are shown at rest, during maximal exercise and during hyperaemia. * denotes a significant change from rest value ($p \leq 0.05$); ** denotes a significant change from rest value ($p \leq 0.01$). In determining the change from rest values during hyperaemia, the rest2 period is used. This is not shown for clarity.*
HR, heart rate, SBP, systolic blood pressure; DBP, diastolic blood pressure; AI, augmentation index; DTF, diastolic time fraction; RPP, rate pressure product; APV, average peak velocity; VTI, velocity time integral; VTI.min, product of VTI and heart rate; MR, micro-vascular resistance; MR_{DIAS}, diastolic micro-vascular resistance; MG_{NET} pressure gradient across the aortic valve accounting for pressure recovery; LV pressure, left ventricular pressure; mRPP, modified rate pressure product; CO, cardiac output; P_d/P_a, the ratio of distal coronary artery pressure and aortic pressure.

3.4.3 External and Myocardial Work

Controls performed more external work (Watts) than patients with AS during the catheterization laboratory exercise protocol (98 ± 25W vs. 77 ± 20W, p = 0.005).

The mean external work (Watts) performed in the catheterization laboratory compared to the stress echocardiography protocol was similar in the 13 patients who had both procedures (78 ± 24W vs. 88 ± 28W, p = 0.07).

The cardiac output at rest in the 13 AS patients who underwent stress echocardiography was 5.4 ± 1.6l.min^{-1} and rose to 9.3 ± 2.5 l.min^{-1} during maximal exercise (p < 0.001). Resting LV pressure was 177 ± 27mmHg rising to 243 ± 38mmHg on exercise (p < 0.001).

Myocardial work, estimated as RPP, was significantly higher for AS patients than controls, at rest (9707 ± 2925 vs. 12721 ± 3399 mmHg.min^{-1} respectively, p = 0.003) as well as during peak exercise (20841 ± 7622 vs. 27467 ± 7260 mmHg.min^{-1}, p = 0.02).

3.4.4 Wave Intensity Analysis

The absolute magnitude and percentage contribution of each of the four dominant waves is shown in table 3.3. The magnitude of each of the waves increased, in controls and AS patients, in response to exercise. The percentage increase in the dominant BCW was less in controls compared to AS: 99%(11-320) vs. 296%(115-821), p= 0.005 (figure 3.1). There were no other significant differences between groups in the relative change of any of the other waves from rest to exercise.

With hyperemia the magnitude of the FCW and the BEW increased in the control group. There was no significant increase in the BCW. In the AS group there was a significant rise in BCW, FCW and BEW (table 3). The percentage change in the BCW was less in controls compared to AS patients: 25% (-40-82) vs. 112% (25-231), p = 0.008 (figure 3.1) and the percentage change in FCW was greater in controls compared to AS: 164 (95-332) vs. 67 (19-148), p = 0.004. There were no other significant differences in the percentage change of any of the other waves from rest to exercise or rest2 to hyperemia

	Rest			Maximal Exercise			Hyperaemia		
	Control	**Aortic Stenosis**	**P-value**	**Control**	**Aortic Stenosis**	**P-value**	**Control**	**Aortic Stenosis**	**P-value**
	Coronary Wave Intensity Analysis, x 10^5 mmHg.m-2.s-2								
BCW	6.8 (3.7-9.6)	3.3 (2.2-4.4)	< 0.001	9.9 (7.8-17.5)**	13.3 (9.1-27.9)**	0.22	8.0 (5.3-10.7)	9.6 (5.5-16.9)**	0.2
FCW	4.2 (2.4-7.1)	2.3 (2.0-3.6)	0.046	16.6 (6.7-33.2)**	11.6 (7.2-15.4)**	0.2	13.4 (7.5-22.3)**	7.3 (4.9-11.0)**	0.02
FEW	0.7 (0.3-1.5)	0.4 (0.1-1.0)	0.19	4.7 (2.3-9.2)**	4.0 (2.1-11.0)**	0.83	0.8 (0.3-3.6)*	1.5 (0.4-4.1)	0.76
BEW	11.2 (8.1-23.8)	12.3 (8.6-20.0)	0.88	29.5 (9.2-72.5)**	43.2 (24.9-71.7)**	0.62	21.2 (11.3-48.8)**	23.6 (14.3-35.6)*	0.95
	Percentage Contribution to total Wave Intensity, %								
BCW	28 ± 14	15 ± 7	0.001	19 ± 13	20 ± 8*	0.69	17 ± 10**	24 ± 12**	0.034
FCW	17 ± 8	14 ± 4	0.01	23 ± 8	17 ± 9	0.043	29 ± 9**	18 ± 8*	<0.001
FEW	4 ± 4	5 ± 9	0.43	9 ± 8*	7 ± 6	0.46	5 ± 7	5 ± 6	0.72
BEW	52 ± 13	66 ± 9	<0.001	50 ± 18	56 ± 11**	0.3	49 ± 13	52 ± 14**	0.51

*Table 3.3: Absolute magnitude and percentage contribution to total wave intensity of the four dominant coronary waves identified by wave intensity analysis at rest, on maximal exercise and during hyperaemia. Values are expressed as medians and interquartile ranges. Backward compression wave, BCW; Forward compression wave, FCW; Forward expansion wave, FEW; Backward expansion wave, BEW. * denotes a significant change from rest value ($p \leq 0.05$); ** denotes a significant change from rest value ($p \leq 0.01$). In determining the change from rest values during hyperaemia, the rest2 period is used. This is not shown for clarity.*

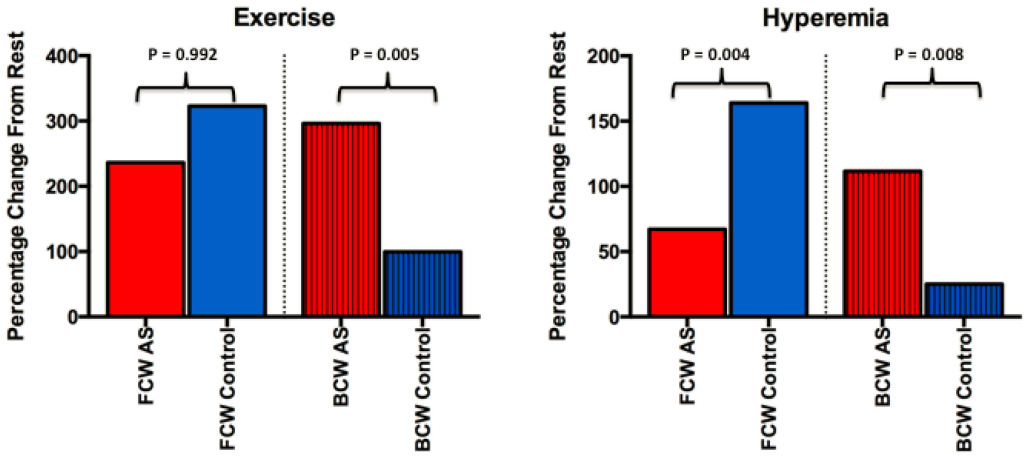

Figure 3.1: The percentage change from baseline in the backward compression wave (BCW) and forward compression wave AS patients (Red) and controls (Blue). For hyperaemia, the rest2 values are used as the resting values. Median values are displayed (non-parametric data).

A typical coronary pressure and flow waveform, with the corresponding WIA curves, at rest and during hyperemia, in a patient with AS is shown in figure 3.2.

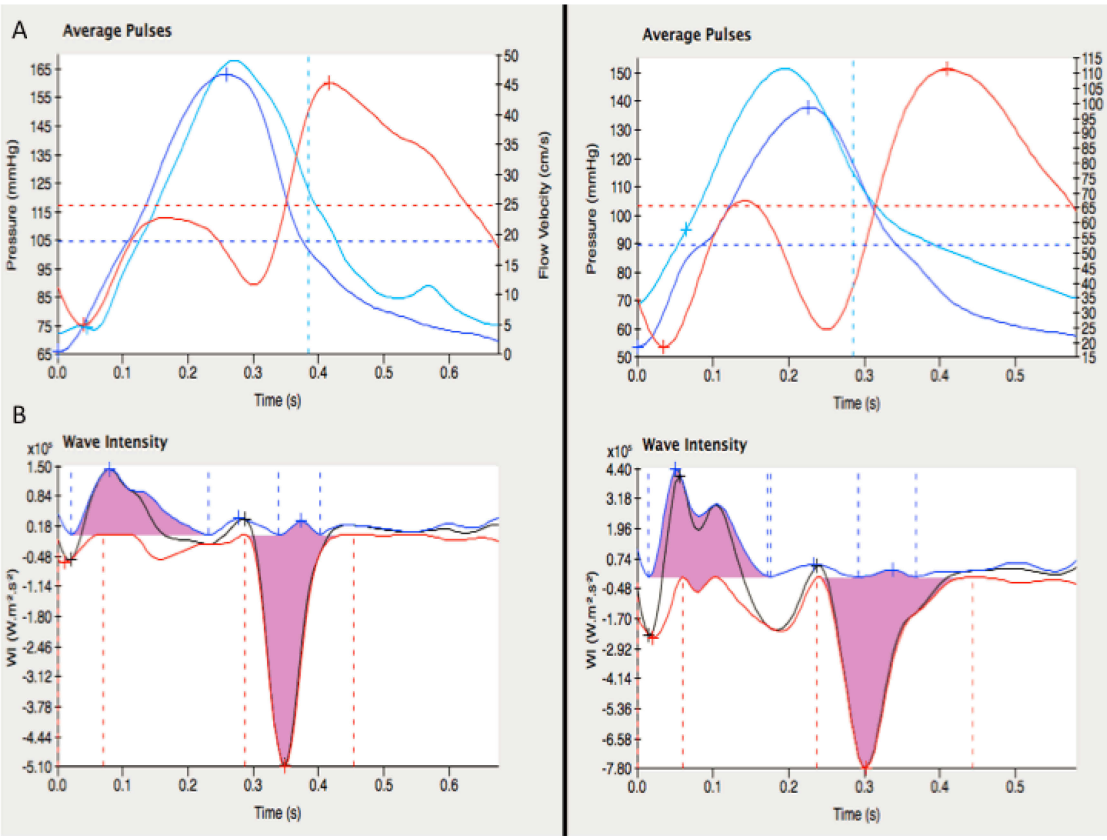

Figure 3.2: Wave Intensity Analysis of a patient with severe symptomatic AS at rest (A) and during hyperaemia (B). Top panels show the ensemble average of 10 consecutive cardiac cycles. Dark blue curve = distal coronary artery pressure; Light blue curve = Aortic pressure; Red curve = distal coronary artery flow velocity.
The bottom panels show the corresponding wave intensity analysis. Black curve = net wave intensity analysis; Blue Curve = Seperated forward waves; Red curve = Seperated backward waves. The shaded areas represent waves that accelerate coronary flow and the un-shaded areas represent waves that decelerate coronary flow. N.B the different scales between the resting and hyperaemic graphs.

This difference in the percentage change in the BCW on exercise and the percentage change in BCW and FCW during hyperemia, led to a change in the balance of accelerating and decelerating waves from rest to exercise and hyperemia. At rest accelerating waves accounted for 70% of the forces driving coronary flow in the control group and 80% in the AS group ($p = 0.005$). On maximal exercise there was no discernable difference between groups (73% vs. 73%, $p = 0.95$) and with the induction of hyperemia the resting pattern had reversed (78% vs. 70%, $p = 0.047$) (figure 3.3).

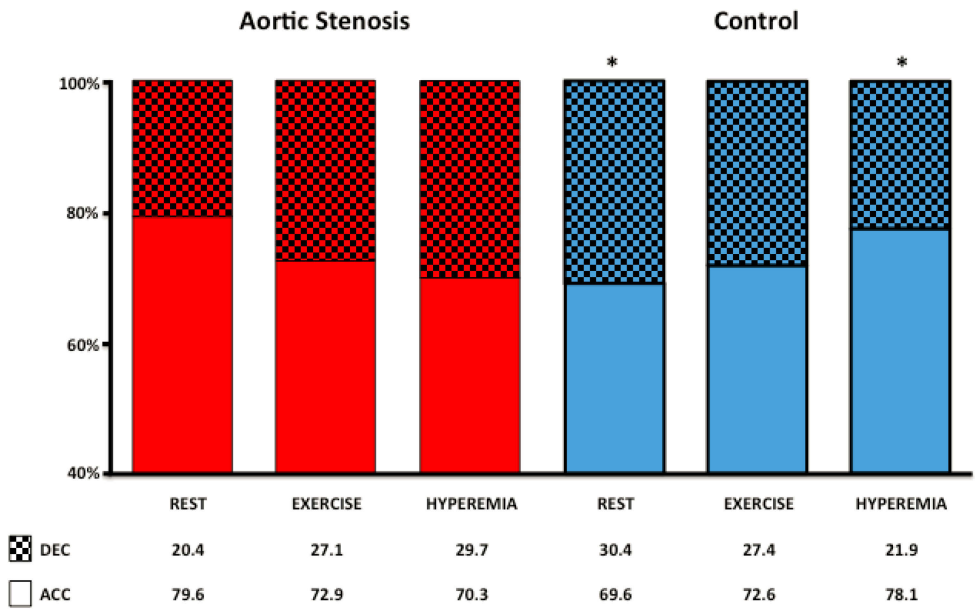

*Figure 3.3: Percentage of total wave intensity that accelerates and decelerates coronary flow at rest, during maximal exercise and hyperaemia for both AS patients and controls. Red bars = decelerating wave intensity; Green bars = Accelerating wave intensity; Ex, maximal exercise; Hyp, Hyperaemia. * denotes $p \leq 0.05$ compared to AS*

Resting echocardiographic markers of AS severity or measures of ventricular systolic and diastolic function did not correlate with absolute values of any of the dominant waves at rest, during maximal exercise or in the hyperemic state.

During hyperemia, EOA correlated with the percentage contribution of the BEW to total WI ($r = 0.637$, $p = 0.006$). The same relationship was observed between the percentage contribution of all accelerating waves and EOA ($r^2 = 0.36$, $p = 0.01$) (figure 3.4).

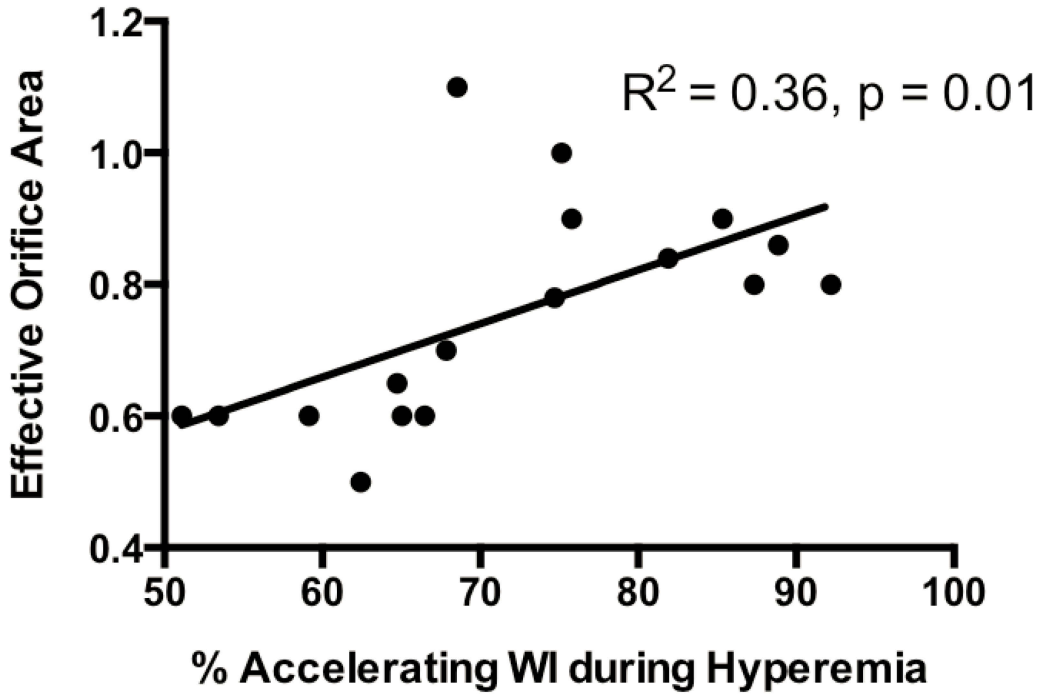

Figure 3.4: Relationship between effective orifice area and the percentage contribution of accelerating waves to total wave intensity (WI) during hyperaemia.

3.5 Discussion

3.5.1 Main Findings

The main finding of this study is that patients with AS fail to alter their coronary flow in proportion to the increase in cardiac work, making the myocardium vulnerable to ischemia during conditions of stress. The inability to adequately augment coronary flow is secondary to a pathophysiological imbalance of forces accelerating and decelerating coronary flow in AS during stress. While the efficiency of the healthy heart improves during exercise and hyperemia, the reverse is observed in AS.

3.5.2 Response of the healthy heart to stress

During exercise, skeletal muscle requirements for oxygen increase. This increase in demand is met by local vasodilatation of resistance vessels and an increase in cardiac output[51]. In providing this increase in cardiac output, there is an increase in each of the three major determinants of myocardial oxygen demand: heart rate, contractility and myocardial work[145],[146],[147]. The corresponding requirement for additional myocardial oxygen supply has to principally be met by increases in coronary blood flow due to the high basal level of myocardial oxygen extraction (70-80%)[63]. Coronary blood flow is determined by perfusion pressure and microvascular resistance (MR), both of which change throughout the cardiac cycle due to the phasic effects of the beating heart on the microvasculature. This intimate relationship between cardiac contraction and coronary flow is often referred to as cardiac-coronary coupling. The contracting myocardium compresses the intramural coronary vasculature, increasing the downstream pressure and leading to a reduction in

perfusion pressure and an increase in MR[148]. MR can be divided into two components: Firstly due to intrinsic properties of the resistance vessels, the vascular resistance; secondly due to mechanical compression of the resistance vessels, the compressive resistance. Measuring MR during mid to late diastole, where myocardial compressive forces are at their lowest[128] allows insight into the vascular component of MR.

In response to exercise we found a significant increase in heart rate, arterial blood pressure and myocardial work (RPP). A corresponding increase in coronary flow was seen with a reduction in coronary MR. Furthermore, MR_{DIAS} falls by a greater degree than pan-cardiac cycle MR, demonstrating that a drop in vascular resistance compensates for the increase in systolic compressive resistance during exercise.

Hyperemia augments coronary blood via different mechanisms to exercise; it is associated with a more modest increase in HR and a more marked reduction in MR. An important observation is that minimum MR and in particular minimum MR_{DIAS} was lower with hyperemia than with exercise signifying that despite exercising patients to exhaustion, some microvascular reserve remained. Overall, coronary blood flow was increased to a greater degree with hyperemia than with exercise.

Wave intensity analysis, a time domain method of analysis, provides directional, quantitative and temporal information of cardiac-coronary coupling. In response to exercise the magnitude of each of the 4 dominant waves increases which is consistent with previous studies in patients without AS[149]. This increase likely reflects the increase in cardiac contractility and more rapid changes in left ventricular pressures during exercise, that then manifest as greater energy fluxes in the coronary

circulation. Although the magnitude of each the 4 waves increase, the relative increase in the accelerating forward compression wave, originating from the aorta, is greatest. This has the overall effect of increasing the percentage contribution of accelerating waves to total WI and hence improved efficiency in coronary flow.

In response to hyperemia, the magnitude of the accelerating FCW and BEW as well as the decelerating FEW increased in keeping with findings in non-human studies[150],[151]. Hyperemia leads to an increase in the vascular diameters via smooth muscle relaxation and hence larger vascular volumes[148]. Therefore the force of cardiac contraction and relaxation is transmitted to a greater degree to the microvasculature and leads to greater changes in pressure and flow[152]. More fundamentally, maximal vasodilation gives a window into ventricular mechanics by minimizing the effect of vasomotor tone on WIA and maximizing the transmission of ventricular forces. As with exercise, the large relative increase in the accelerating FCW shifts the balance of forces in favor of accelerating waves and improving the efficiency of coronary flow.

3.5.3 Response to Stress in Aortic Stenosis

In AS, under resting conditions, there is a resting supply/demand imbalance relative to the normal heart, evidenced by similar coronary blood flow in the presence of greater myocardial work in AS than in controls. This has been demonstrated previously[153],[154]. As with controls, coronary blood flow increases during exercise in AS but as myocardial work is much greater in the latter group, the

imbalance of supply and demand worsens. making the myocardium more vulnerable to ischemia.

Microvascular resistance was lower at rest in patients with AS than healthy controls, particular the vascular component, MR_{DIAS}. This goes some way to explain diminished flow reserve[47] (on exercise as well as hyperemia) in AS patients, as there is resting microvoascular dilation which impairs the capacity to further reduce MR in response to stress; a finding that is consistent with previous studies[23]. Microvascular resistance falls to a greater degree with hyperemia than it does with exercise and this relative change in MR is less in AS than in controls. During maximal hyperemia the MR_{DIAS}, that is lower at rest in AS than in controls, is similar to that of controls. This indicates a normal minimal vascular resistance in AS and thereby supports the hypothesis that it is abnormal cardiac-coronary coupling, rather than fundamental differences in microvascular function, that is responsible for reduced blood flow in AS.

Wave intensity analysis revealed differences in the forces governing coronary flow at rest, during exercise and on maximal hyperemia that could not be appreciated with pan-cardiac cycle measures. The BEW is the largest of the coronary waves, provides the principal force driving coronary flow and has received the most attention in previous studies[155],[149],[156]. This early diastolic wave is generated by the reduction in the mechanical microvascular resistance, caused by falling LV pressure. Davies et al[144] studied coronary WIA in patients with severe AS undergoing trans-catheter aortic valve insertion (TAVI). This study reported a correlation between the peak BEW (absolute magnitude) and peak aortic valve gradient at rest. With pacing

the magnitude of the BEW fell. A fall in the BEW with exercise or hyperemia was not observed in our study; pacing however represents a physiologically different form of stress.

The backward compression wave (BCW) occurs in early systole during the period of isovolumic contraction, when the aortic valve is closed. This wave originates in the microcirculation and travels retrogradely along the coronary artery. It is produced from the transmission of rapidly rising left ventricular pressure onto the intramural vessels. This compression causes a rise in distal coronary pressure and decelerates antegrade coronary flow. Its magnitude is determined by cardiac contractility, rate of change of LV pressure and the degree of transmission of this pressure to the intramural vasculature.

Under conditions of exercise there is a fall in microvascular resistance with large increases in cardiac contractility and LV pressures that act to increase cardiac-coronary coupling. During hyperemia, the even greater reduction in micro-vascular resistance has the same effect. It is suggested that this increased cardiac-coronary coupling leads to the high left ventricular pressures in AS being better transmitted to the coronary vessels and manifesting as large relative changes in the BCW during stress.

Another of the important finding of our study was that the increment in the FCW during hyperemia was attenuated in AS compared to controls. This wave originates in the ventricle and travels via the aorta into the coronary circulation. The main driving force for the FCW is ventricular contraction. In the presence of AS, the pressure drop across the aortic valve has the effect of reducing the rate of change in pressure and

flow that is transmitted along the coronary artery, hence attenuating the FCW. In addition the relative fall in MR was decreased in AS compared to controls (as greater systolic compressive forces during systole, counteract the fall in diastolic vascular resistance), which also attenuates the FCW.

It should be noted that the magnitude of WI is not proportional to coronary flow. It is the relative balance of accelerating and decelerating waves that is of primary importance in determining coronary flow. WI is greatest during exercise, however coronary flow is greater during hyperemia. In this study we have shown that under conditions of stress, in the normal heart, coronary perfusion becomes more efficient, measured by an increasing percentage of accelerating waves. The exact opposite is true in severe AS, where coronary perfusion becomes less efficient with exercise and hyperaemia.

3.5.4 Clinical Implications

With the onset of stress, patients with AS are unable to augment coronary flow in response to the increase in myocardial work creating an environment vulnerable to ischemia which provides a possible mechanism for exercise induced angina and peri-operative cardiac events. This inability to adequately augment coronary flow is due to a pathophysiological imbalance of forces accelerating and decelerating coronary flow in AS during stress. Furthermore those with the most severe AS (measured by EOA) are at the highest risk of ischemia.

Although changes in cardiac mechanics are much greater during exercise, hyperemia increases the sensitivity of the coronary circulation to myocardial contraction. Therefore one may postulate that patients with AS may become particularly vulnerable ischemia during periods of profound vasodilatation and increased myocardial oxygen demand, such as during anesthesia rather than during exercise.

3.5.5 Limitations

This was a single center study with relatively modest numbers of patients in each group, although it the largest invasive exercise coronary physiology cohort that has been reported to date and the first to have been performed in patients with AS during exercise.

Another limitation of this study is that AS and control groups were not perfectly matched. While patients with AS were older than the controls, we found no correlation between age and absolute values of WI, relative changes in WI or the total percentage of accelerating or decelerating WI under any of the three conditions. Furthermore, wherever possible, we have controlled for differences in baseline parameters by looking at individual's percentage changes with exercise and hyperemia.

We were unable to measure left ventricular pressure simultaneously with coronary physiological data in AS patients and instead, were limited to measuring the former during a separate period of exercise, using an identical exercise protocol. Future

studies of this nature would be strengthened by the simultaneous assessment of ventricular dynamics and coronary physiology.

We have calculated wave speed using the single point method, during hyperemia the wave speed estimated using this method might differ from the true wave speed[157].

3.5.6 Conclusion

In response to stress (exercise and hyperemia), patients with severe AS have an attenuated rise in forces that accelerate coronary flow and an augmented rise in the forces that decelerate flow. This is coupled with an excess of myocardial work compared to controls. This pathophysiological response provides a mechanism for the reduced coronary flow reserve seen in AS and hence angina symptoms and the elevated rate of myocardial infarction during non-cardiac surgery. The degree of this imbalance is correlated with the severity of AS.

Chapter 4: Coronary Microvascular Disease: Impaired Flow and Impaired Efficiency

4.1 Abstract

Introduction

Patients with coronary microvascular disease (MVD) have an unfavorable prognosis, even in the absence of obstructive epicardial coronary disease. The pathophysiological basis of increased cardiac events is unclear.

Methods and Results

A total of 51 patients with FFR values > 0.8 were enrolled. They were divided into two groups: patients with MVD (CFR < 2.0) and controls (CFR ≥ 2.0). Simultaneous intracoronary pressure and flow velocity recordings were made, at rest, during supine bicycle exercise and during hyperemia. Wave intensity analysis was used to quantify waves that accelerate and decelerate coronary flow. At rest coronary flow was higher (1369±403 vs. 874±309, $p < 0.001$) and microvascular resistance was lower (464±124 vs. 748±265, $p < 0.001$ in patients with MVD compared to controls. In response to hyperemia and exercise, the relative reduction in microvascular resistance was less in MVD compared to controls (23±30% vs. 69±10%, $p < 0.001$ and 6±20% vs. 37±18%, $p = 0.003$ respectively). In response to exercise and hyperemia, the percentage contribution of accelerating waves to total wave intensity decreased in MVD, hence coronary perfusion efficiency decreased. The opposite was seen in controls.

Conclusion

The resting vasodilatation and elevated coronary flow at rest in MVD is suggestive of disordered autoregulation. In response to stress, patients with MVD have a lower reduction in microvascular resistance, which limits their ability to augment flow. In

addition to reduced maximal flow, there is a reduction in coronary perfusion efficiency.

4.2 Introduction

It is frequent to encounter patients with evidence of myocardial ischemia without visible atherosclerosis on invasive coronary angiography. Many patients who present in this fashion will have evidence of structural heart disease, such as aortic stenosis, left ventricular hypertrophy secondary to arterial hypertension or infiltrative heart disease. However, many will have no evidence of structural heart disease. Conversely many patients with severe obstructive coronary lesions never experience symptoms or have evidence of myocardial ischemia [158][159]. Therefore there is an absence of a direct relationship between obstructive coronary artery disease and ischemic heart disease. The obstructive coronary plaque represents only a single manifestation of the atherosclerotic disease process. A number of other mechanisms exist that are capable of inducing myocardial ischemia: spontaneous thrombus; coronary vasospasm; inflammation; microvascular dysfunction and endothelial dysfunction [160][88]. As a result there is a growing consensus that the focus in ischemic heart disease should be shifted from a plaque-centric approach towards the microvasculature and myocardial cell[161].

Coronary microvascular disease (MVD) describes abnormalities in vasomotor tone or metabolic regulation of the coronary arterioles, which are the main determinants of coronary vascular resistance. The pathophysiology is complex and involves endothelium-dependent and independent mechanisms, as well as structural changes in the vessel wall[162][88].

Patients with coronary microvascular disease (MVD) have an unfavorable prognosis, even in the absence of obstructive epicardial coronary disease[89]. The pathophysiological basis of increased cardiac events is unclear. The aim of this study was to characterize the forces that govern coronary flow and myocardial perfusion at rest and during stress.

4.3 Methods

A detailed description of the cardiac catheterization protocol, haemodynamic analysis and exercise protocol can be found in the methods chapter (chapter 2). Only the patient selection and group allocation is described below.

4.3.1 Patient Selection

Patients presenting with chest pain syndromes referred for coronary angiography were recruited to the study. They were eligible if they had preserved left ventricular systolic function (left ventricular ejection fraction > 50%) and either angiographically epicardial coronary arteries or had a lesion of equivocal significance in a single vessel coronary. Exclusion criteria were: any contraindication to adenosine; the presence of valve disease (> mild on echocardiography); history of syncope; recent acute coronary syndrome or presentation with heart failure (within 4 weeks) or any comorbidity that may influence exercise tolerance. The study protocol was approved by the institutional research ethics committee (NHS REC reference: 12/LO/1787). All of the participants were provided with an information sheet detailing the study protocol before obtaining informed consent.

4.3.2 Allocation of Groups

Patients were dichotomized by FFR in two groups: > 0.80 and ≤ 0.8. They were also dichotomized by CFR: ≥ 2.0 and < 2.0. Based on the values of FFR and CFR the patients were further allocated to one of four groups: those with concordant normal FFR and CFR values (FFR > 0.80 and CFR ≥ 2.0); discordant FFR and CFR values,

predominant epicardial disease (FFR ≤ 0.8, CFR ≥ 2.0); discordant, predominant microvascular disease (FFR > 0.80, CFR < 2.0) and concordant abnormal FFR and CFR (FFR ≤ 0.8, CFR < 2.0). A study flow chart is shown in figure 4.1.

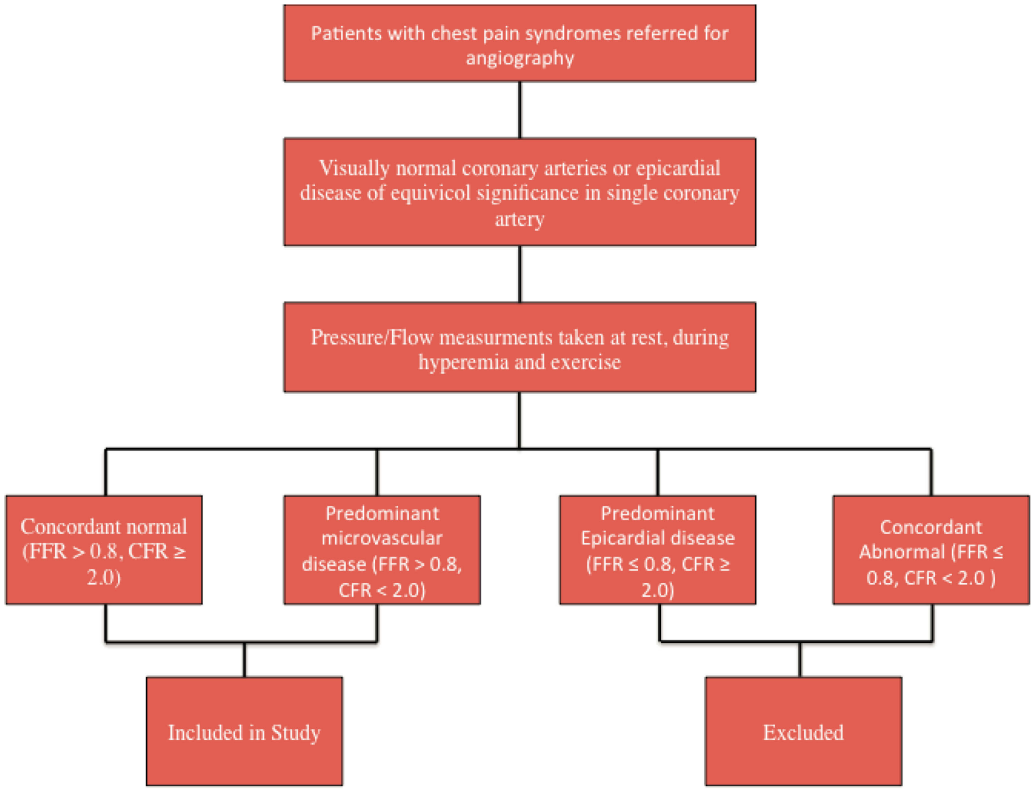

Figure 4.1: Study flow chart

4.4 Results

4.4.1 Patient Characteristics

A total of 51 patients were recruited into the study. Of these patients, 41 had an FFR of > 0.80 and 10 had an FFR of ≤ 0.8. A scatter plot of FFR against CFR is shown in Figure 4.2. A total of 25 patients had concordant normal FFR and CFR values; 4 patients had discordant FFR and CFR values indicative of predominant epicardial disease (FFR ≤ 0.8, CFR ≥ 2.0); 16 patients had discordant FFR and CFR values indicating predominant microvascular disease (FFR > 0.80, CFR < 2.0); 6 patients had concordant abnormal FFR and CFR values. A total of 20 patients (39%) had discordant FFR and CFR values. There was no correlation between CFR and FFR ($r = 0.16$, $p = 0.26$). The primary focus of this study was on patients with microvascular dysfunction, hence the predominantly epicardial disease group and the concordant abnormal group are excluded from further analysis.

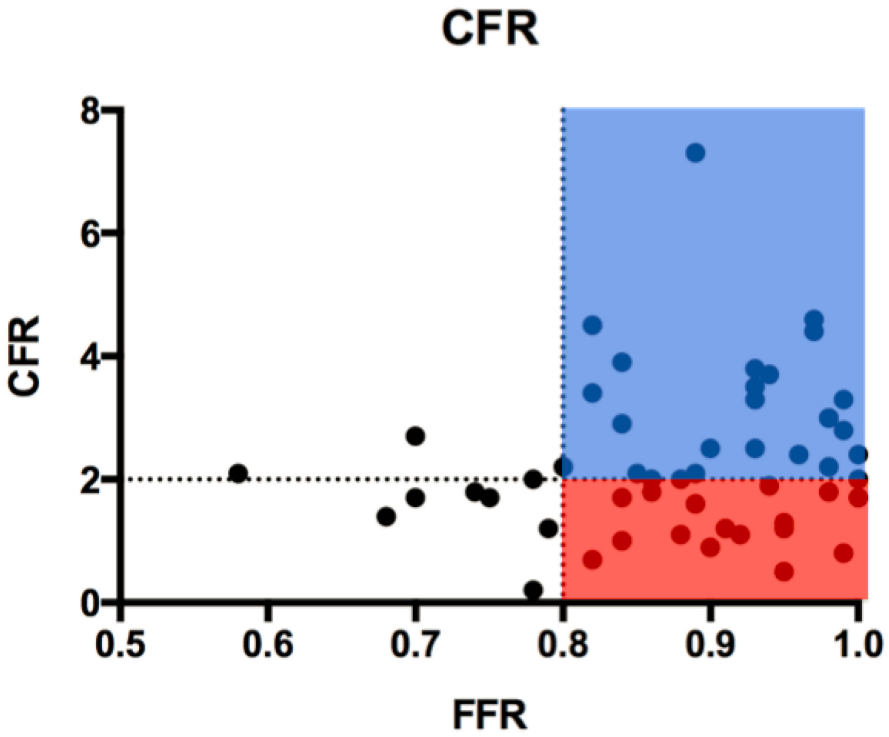

Figure 4.2: Scatter plot of CFR vs. FFR. Horizontal dotted line dichotomizes CFR values at 2.0 and a dotted vertical line dichotomizes FFR at values of 2.0. The blue shaded area represents all FFR values > 0.80 and CFR ≥ 2.0. The red shaded area represents values of FFR > 0.8 and CFR < 2.0.

The remaining 41 patients consisted of 25 controls and 16 patients with predominant microvascular disease, MVD patients. The patient demographics are shown in table 4.1.

	Controls	MVD	p-value
Number of patients	25	16	
Male, n (%)	21 (84)	14 (88)	0.76
Age, years	60±10	65±12	0.21
Hypertension, n (%)	14 (56)	11 (69)	0.41
Hypercholesterolaemia, n (%)	19 (76)	14 (88)	0.37
Diabetes, n (%)	5 (20)	4 (25)	0.71
Smoker, n (%)	10 (40)	4 (25)	0.32
Family History of CAD, n (%)	9 (36)	7 (44)	0.62
Previous MI, n (%)	3 (12)	7 (44)	0.021
Previous PCI, n (%)	5 (20)	5 (31)	0.41

Table 4.1: Demographics of control and microvascular disease patients. CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

4.4.2 Pan-cardiac cycle data

Pan-cardiac cycle data in both the controls and the MVD patients are shown in table 4.2.

At rest the diastolic time fraction was greater in controls compared to MVD. Cardiac work was similar in both cohorts.

All measures of coronary flow were greater in MVD patients compared to controls at rest and both the MR and diastolic microvascular resistance (MR_{DIAS}) were less in MVD compared to controls.

With the induction of hyperemia the HR increased and the systolic and diastolic blood pressure fell in both groups of patients. There was a fall in DTF ($p = 0.001$) and rise in RPP in controls ($p = 0.007$). These indices did not change in MVD patients

VTI.HR increased with hyperemia in both groups. MR and MR_{DIAS} fell in both groups. The relative reduction in MR from rest to hyperemia was less in controls compared to MVD (23±30% vs. 69±10%, $p < 0.001$).

In response to exercise, the heart rate (HR), systolic blood pressure and rate pressure product (RPP) increased in both groups.

Coronary flow, measured by VTI.HR, increased in controls ($p = 0.01$) but there was no change in the MVD patients ($p = 0.36$).

Both MR and MR_{DIAS} decreased in controls ($p = 0.01$ and $p = 0.024$). There was no change in MR or MR_{DIAS} in MVD ($p = 0.40$ and $p = 0.17$). The relative reduction in MR from rest to maximal exercise was less in controls compared to MVD (6±20% vs. 37±18%, $p = 0.003$).

The exercise CFR was 1.8±0.5 in controls vs. 1.1±0.2 in MVD patients, $p = 0.004$.

	Rest			Hyperemia			Exercise		
	Controls	**MVD**	**p-value**	**Controls**	**MVD**	**p-value**	**Controls**	**MVD**	**p-value**
Number of patients	25	16		25	16		5	7	
	Aortic Hemodynamics								
HR, bpm	75±16	74±12	0.99	87±20*	86±18*	0.87	135±36*	119±15*	0.31
SBP, mmHg	131±23	144±24	0.09	126±22*	126±27*	0.94	156±43*	170±11*	0.41
DBP, mmHg	78±15	76±13	0.69	70±12*	73±16	0.59	87±14	93±8*	0.33
DTF	0.60±0.08	0.55±0.06	0.05	0.53±0.8*	0.52±0.07	0.52	0.45±0.06	0.41±0.06*	0.25
RPP, bpm.mmHg	9730±2626	10698±2168	0.23	10910±3173*	10654±2559	0.79	21036±7384*	20249±2371*	0.79
	Coronary Hemodynamics								
APV, cms^{-1}	14.6±5.1	22.8±6.7	<0.001	43.5±13.7*	28.7±13.5*	0.002	25.8±9.6*	21.5±4.0	0.31
VTI, cm	12.1±4.4	18.9±6.4	<0.001	31.6±11.8*	21.1±10.4	0.006	12.3±5.8	11.0±2.6*	0.61
VTI.HR, $cm.min^{-1}$	874±309	1369±403	<0.001	1546±576*	1292±240*	0.31	2608±821*	1722±809	0.002
MR, $mmHg.cm^{-1}.s^{-1}$	748±265	464±124	<0.001	218±69*	363±184*	0.001	491±197*	566±152	0.47
MR_{DIAS}, $mmHg.cm^{-1}.s$	549±216	316±91	<0.001	139±52*	220±115*	0.004	321±147*	3.11±100	0.89

*Table 4.2: Pan-cardiac cycle hemodynamics (Aortic and Coronary) of control and MVD patients, at rest, during hyperemia and at maximal exercise. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure, DTF, diastolic time fraction; RPP, rate pressure product; APV, average peak velocity; VTI, velocity time integral; VTI.HR, product of the velocity time integral and heart rate; MR, microvascular resistance, MR_{DIAS}, diastolic microvascular resistance; P_d/P_a, the ratio of distal coronary artery pressure and aortic pressure. * represents a significant change from resting conditions within each group ($\alpha = 0.05$). In determining the change from rest values during hyperaemia, the rest2 period is used. This is not shown for clarity.*

4.4.3 Wave Intensity Analysis and Coronary Perfusion Efficiency

The absolute magnitude and percentage contribution to total wave intensity (WI) of each of the four dominant waves at rest, during hyperemia and on maximal exercise is shown in table 4.3.

Under resting conditions the magnitude of the FCW, BEW and FEW was smaller in controls compared to MVD patients.

In response to hyperemia, the magnitude of all four dominant waves in the control group increased. In patients with MVD, only the magnitude of the BCW increased from baseline conditions.

The percentage change in the FCW and the BEW was greater in controls compared to MVD patients 279% [(112 to 530%) vs. 34% (-17 to 96%), $p < 0.001$ and 137% (71 to 192%) vs. -20% (-55 to 17%), $p < 0.001$ respectively]. As a result, during hyperemia, the absolute magnitude of the FCW and BEW is greater in controls compared to MVD patients, the opposite pattern that was seen under resting conditions.

In response to exercise a similar pattern was observed. There was an increase in the magnitude of each of the four dominant waves in controls but not in MVD patients. The percentage increase in the FCW and BEW was greater in controls [(388% (202 to 720%) vs. 24%(-67 to 234%), $p = 0.048$ and 147% (70 to 613%) vs. 27% (-33 to 132%), $p = 0.048$ respectively)].

	Rest			Hyperemia			Exercise		
	Controls	MVD	p-value	Controls	MVD	p-value	Controls	MVD	p-value
Number of patients	25	16		25	16		5	7	
	Coronary Wave Intensity, x 105 mmHg.m-2.s-2								
FCW	3.4(2.0-6.6)	6.0(3.6-11.0)	0.009	13.2(7.8-17.7)*	7.2(4.0-13.8)	0.08	16.7(12.6-49.5)*	8.1(2.0-26.2)	0.15
BEW	10.1(6.6-15.4)	17.9(13.5-32.9)	0.005	22.2(15.5-40.5)*	15.5(8.8-21.1)	0.03	29.5(15.8-138.9)*	18.0(16.3-47.2)	0.43
BCW	5.9 (4.1-7.8)	6.6(3.6-10.0)	0.61	8.9(5.3-13.3)*	8.9(5.3-13.3)*	1	10.0(8.2-22.0)*	9.0(7.5-15.7)	0.53
FEW	0.5(0.2-1.4)	1.8(1.1-3.3)	<0.001	1.1(0.3-3.9)*	1.8(0.9-4.6)	0.18	3.8(1.4-10.7)*	4.7(3.4-10.5)	0.64
	Percentage Contribution to Total Wave Intensity, %								
FCW	17±8	18±6	0.59	25±11	23±9	0.54	27±7	17±10	0.1
BEW	51±14	56±13	0.3	50±13	43±13	0.1	49±21	48±12	0.94
BCW	29±13	20±9	0.03	20±11	27±15	0.12	17±7	23±16	0.45
FEW	4±4	6±5	0.06	5±7	7±6	0.24	7±9	12±7	0.37
Accelerating	68±15	74±12	0.18	75±15	66±17	0.09	76±14	65±18	0.3

*Table 4.3: Absolute magnitude and percentage contribution to total wave intensity of the four dominant coronary waves identified by wave intensity analysis at rest, on maximal exercise and during hyperaemia. Values of wave intensity are expressed as medians and interquartile ranges. Values of percentage contribution are expressed as mean±standard deviation. Backward compression wave, BCW; Forward compression wave, FCW; Forward expansion wave, FEW; Backward expansion wave, BEW. * denotes a significant change from rest value ($p \leq 0.05$). In determining the change from rest values during hyperaemia, the rest2 period is used. This is not shown for clarity.*

The percentage contribution of accelerating waves to the total WI at rest was 74±12% in MVD patients and 68±15% in controls, p = 0.18. During maximal hyperemia the value decreased in MVD (increased perfusion efficiency) and increased in controls (66±17 vs. 75±15, p = 0.09). This same discordant change in efficiency was seen with hyperemia (65±18 vs. 76±14, p = 0.30)(figure 4.3). The change in the percentage of accelerating waves to total wave intensity during hyperemia was different between MVD and controls (-8±14 vs. 7±18, p = 0.007).

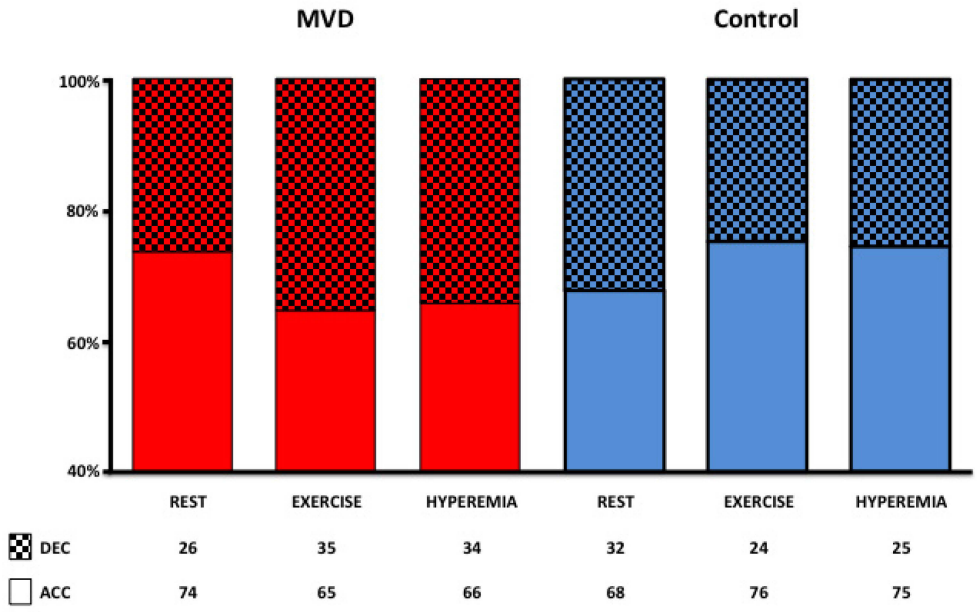

Figure 4.3: Percentage of total wave intensity that accelerates and decelerates coronary flow, at rest, during maximal exercise and hyperemia for both microvascular disease (MVD) patients and controls. Red bars = MVD; Blue bars = Control Patients; Checkerboard pattern = Decelerating Wave Intensity; Plain Bars = Accelerating Wave Intensity.

4.5 Discussion

4.5.1 Main Findings

The primary findings of this study are:

- Patients with MVD have resting vasodilatation and elevated coronary flow and lower microvascular resistance
- In response to stress, this cohort has a smaller relative reduction in microvascular resistance and hence attenuated flow augmentation
- This dysfunctional coronary microcirculation not only reduces maximal coronary flow, but also impairs coronary perfusion efficiency. These processes render the myocardium more susceptible to ischemia.

4.5.2 FFR-CFR discordance: spectrum of Coronary Artery Disease

Previous studies have found similar rates of discordance (31-37%) between FFR and CFR as seen in this study[163][164][89]. The key to understanding this discordance lies in the underlying physiology and assumptions that both FFR and CFR are founded on. The pressure drop that occurs across an epicardial stenosis is determined by the sum of the viscous losses (Poiseuille's law) and losses owing to flow acceleration through the stenosis (Bernoulli's law). These losses increase with the square of the flow velocity: the resulting relationship between pressure and flow is curvilinear rather than linear, as assumed by FFR. The relationship between pressure and flow velocity therefore takes the form:

Equation 4.1 $\Delta P = AU + BU^2$

Where ΔP is the pressure drop as the stenosis, U is the flow velocity. A and B are functions that are determined by the unique properties of the stenosis and the rheological properties of the blood. As hyperemic flow across a lesion increases, the pressure drop across the lesion increases: P_d/P_a and CFR therefore move in discordant directions. A practical example of this phenomenon is the administration of increasing adenosine doses until maximal vasodilation occurs. Prior to maximal hyperemia a lesion may have an P_d/P_a value > 0.80 but CFR < 2.0. With a greater fall in MR flow velocity increases (and hence CFR), which results in a greater pressure drop across the lesion and a smaller value of P_d/P_a (FFR) (figure 4.4).

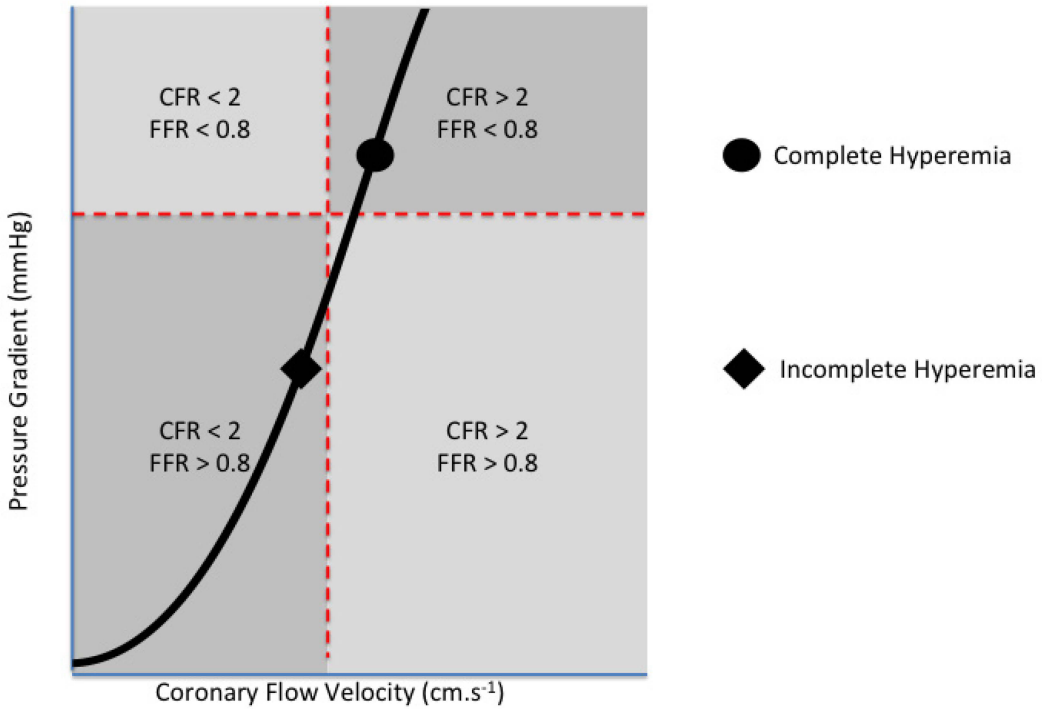

Figure 4.4. The effect of varying degrees of microvascular resistance on fractional flow reserve (FFR) and coronary flow reserve (CFR). It can be seen that by reducing the degree of microvascular resistance (increasing level of hyperemia), FFR and CFR move in discordant directions.

In the presence of appropriate hyperemia, discordant FFR and CFR values do not imply that one is incorrect; rather they provide differing information. It informs on the presence and relative balance of diffuse versus focal atherosclerotic disease and small-vessel disease[165].

An abnormal CFR in the presence of a normal FFR implies the presence MVD. The presence of an abnormal FFR (≤ 0.8) indicates the presence of an epicardial stenosis. If this occurs with a normal CFR value, this indicates that the microcirculatory function is intact and despite the epicardial stenosis, the vessel is able to increase flow substantially in response to demand. The combination of an abnormal CFR in the

presence of a normal FFR can also be caused diffuse coronary artery disease (CAD); as blood flow acceleration is less, the resultant pressure drop across the epicardial segment is restricted[166]. The presence of abnormal MR in this study makes MVD a more plausible explanation of this FFR/CFR discordance than diffuse CAD.

4.5.3 Regulation of Coronary Blood Flow

Autoregulation refers to the intrinsic tendency of the vasculature to maintain constant blood flow despite changes in perfusion pressure[167]. The endothelium is the main mediator of coronary blood flow regulation: In response to different physiological stimuli either vasodilator substances such as nitric oxide (NO) and prostacyclin or vasoconstrictive substances such as endothelin-1 are released. In the presence of obstructive CAD, there is a reduction in perfusion pressure mediated by the pressure drop across the stenosis. Basal coronary flow is maintained by a compensatory vasodilation of the coronary microcirculation. The more severe the stenosis (and hence the greater pressure drop), the greater degree of vasodilation required to maintain flow. There comes a critical point at which the vasodilatory reserve becomes exhausted and basal coronary flow is compromised (stenosis that obstructs approximately 85% of the luminal diameter)[168]. Following a rapid restoration in perfusion pressure, such as following percutaneous coronary intervention elevated basal levels of coronary flow are well recognized[169][170][171], however these changes are transient, returning to baseline within 6 months[171]. Elevated levels of basal coronary blood flow and reduced basal microvascular resistance in MVD, as seen in this study, have only recently been observed and is associated with a poor long-term prognosis[89][172].

Coronary flow reserve, defined as the ratio of hyperemic to basal flow (flow velocity in this study), can be impaired by either an elevation in basal flow or reduction in peak flow. In the two previous studies reporting reduced basal MR and elevated basal flow, the hyperemic values of MR and flow, were not found to be different to control patients[89][172]. Unique to this study is that hyperemic MR was higher and hyperemic flow was lower in MVD compared to controls, furthermore the relative fall in MR was less in MVD compared to controls. The mechanism of reduced CFR is therefore two-fold: elevated basal flow and failure of hyperemic flow augmentation. Augmentation in coronary blood flow in response to adenosine is caused primarily by direct interaction with A_2 receptors on vascular smooth muscle, and as a result is primarily endothelium independent[173]. Endothelium independent microvascular dysfunction has been shown to be a predictor of cardiovascular events in early atherosclerosis[174], post-PCI[175][176] and acute myocardial infarction[177].

Flow mediated dilation (FMD) secondary to exercise represents an endothelium-dependent form of coronary flow augmentation. We did not observe any difference in absolute levels of coronary flow or MR during exercise. Given the small patient numbers, this may be inadequate statistical power. We did however observe no significant change in the MR from rest to exercise in patients with MVD, but a significant fall in MR in control patients. This abnormal vasomotor response has been observed previously during exercise[85].

4.5.4 Cardiac-coronary coupling/Efficiency

The energy driving coronary flow derives from cardiac contraction and relaxation. In all other circulatory beds the resistance to flow is determined by the vascular tone in the resistance vessels, as a result, resistance is relatively constant throughout the cardiac cycle (resistance is a function of pressure so there is some variation). Unique to the coronary circulation is that cardiac contraction causes compression of intramyocardial arterioles, increasing resistance during systole. Resistance therefore varies throughout the cardiac cycle. This interaction of coronary vasculature and cardiac contraction is often referred to as cross-talk or cardiac-coronary coupling[167]. This resistance is modulated by the microvascular tone. Therefore the same energy that drives coronary flow is responsible for impeding it. The energy driving and impeding coronary flow varies depending on prevailing hemodynamic conditions, cardiac contractility and the neuro-hormonal state. With each unique set of prevailing conditions the relative balance of this energy that accelerates and decelerates flow will differ. This balance gives rise to the concept of coronary perfusion efficiency. The percentage of accelerating wave intensity describes what percentage of energy is utilized in accelerating (driving) opposed to decelerating (impeding) flow. The worsening of coronary perfusion efficiency with stress seen in MVD patients, not only limits the augmentation of coronary flow, but also signifies that more cardiac work is needed to achieve the same flow. With this double detrimental effect on coronary physiology during stress, it is easy to see how patients with MVD may develop an imbalance of myocardial oxygen supply and demand, hence rendering the myocardium ischemic. This reduction in coronary perfusion

efficiency was mainly driven by an attenuated increase in the two dominant accelerating waves, the BEW and FCW.

The BEW is the largest of the four dominant waves and is the primary driver of coronary perfusion. It occurs in early diastole and is determined by the rapid ventricular relaxation releasing the compressive pressure on the intramyocardial arterioles. The forward compression wave, a systolic wave, arises from the force of ventricular contraction being transmitted down the coronary artery whilst the aortic valve is open. The BEW is modulated by ventricular relaxation (diastolic function) and the FCW by systolic function, however both are (as are all waves) sensitive to the degree of vasodilation[151]. We believe the primary reason for this difference is the reduced percentage change in the MR in response to stress. It is possible or even plausible that patients with MVD have early systolic/diastolic dysfunction that is being detected, however we do not have detailed echocardiographic documentation of these parameters. Even in the absence of resting ventricular dysfunction, during exercise, the development of cardiac ischemia may limit systolic and diastolic function and hence attenuate both the BEW and FCW. Resting vasodilatation is also the reason for the higher absolute magnitude of the FCW and BEW at rest in patients with MVD.

4.5.5 Limitations

The main limitation of the study is the modest patient numbers. Increasing numbers would not only increase statistical power but would also allow the characterization of those patients with predominant epicardial disease (FFR $\leq$ 0.8, CFR $\geq$ 2.0) and those with concordant abnormal FFRs and CFRs. The study would also be strengthened if

patients had undergone non-invasive ischemia testing prior to coronary angiography, especially with a modality such as MRI that could distinguish endo and epicardial perfusion during stress.

Detailed echocardiographic assessment at rest, during exercise and during hyperemia would provide valuable insight into whether MVD and control patients have differing ventricular responses to stress.

Only six of the final forty-one patients included in the analysis were female. Important differences exist between men and women in coronary vascular physiology and regulation of vasomotor tone in the microcirculation of males and females[162].

4.5.6 Conclusion

MVD manifests as resting microvascular dilation as well as diminished response to stress. While the normal heart has improved efficiency during hyperemia, in MVD efficiency decreases and as a result, flow augmentation is attenuated. These processes render the myocardium more susceptible to ischemia.

Chapter 5: Cardiac Output Reserve – An Integrated Measure of Afterload and Left Ventricular Function in Aortic Valve Stenosis

5.1 Abstract

Objective: Traditional measures of aortic stenosis (AS) severity correlate poorly with the onset and extent of symptoms. The purpose of the study was to identify an integrated index of afterload and left ventricular function that may improve prediction of exercise capacity and need for surgery in AS.

Methods: 48 patients with moderate-severe AS underwent resting transthoracic echocardiography, modified Bruce exercise treadmill testing, B-type natriuretic peptide measurement and bicycle exercise stress echocardiography.

Results: Cardiac Output Reserve (COR), age, left atrial area, and stroke volume reserve (SVR) correlated most strongly with exercise capacity, while resting echocardiographic measures of AS severity did not correlate. COR was the strongest independent predictor of exercise capacity on multiple linear regression (standardized $\beta = 0.48$, $p = 0.001$).

A total of 12 patients volunteered symptoms and 36 denied symptoms during clinical history. Of these 36, 13 patients had revealed symptoms on exercise.

COR was found to be the best parameter to predict the presence or absence of revealed symptoms on exercise (AUC = 0.96, $p < 0.001$). A cut-off value of 77% was 92% sensitive and 100% specific for identifying the presence of revealed symptoms in apparently asymptomatic patients.

Conclusion: Cardiac output reserve is an independent predictor of both exercise capacity and the best parameter to predict the presence of revealed symptoms in AS. This novel objective index may improve the risk assessment of aortic stenosis.

5.2 Introduction

The outcome in severe aortic stenosis (AS) is poor after the onset of symptoms [178]. However, symptom development may be insidious and may be attributed to the effects of age or reduced physical fitness. Even skillful history taking may fail to elicit significant symptoms. Therefore exercise treadmill testing is indicated to unmask symptoms in apparently asymptomatic patients [122][121] despite concerns about the subjectivity of the distinction between physiological and pathological breathlessness.

Rajani et al[179] found that patients with revealed symptoms on exercise had a blunted rate of rise in stroke volume index and cardiac index, as well as lower values of stroke volume index and cardiac index at peak exercise. BNP, a sign of early left ventricular systolic dysfunction, was found to be the strongest resting predictor of peak cardiac index. This is consistent with the findings of other groups who have shown a reduced left ventricular contractile reserve on exercise to be associated with a high risk of future cardiac events[180][181][182]. Patients identified by an increase in the mean transaortic pressure gradient of > 20mmHg during exercise are also at an increased risk of events[122][183][184].

These measures may interact, since a blunted increase in flow, as a result of reduced contractile reserve, may limit the increase in mean gradient on exercise despite the presence of a poorly compliant aortic valve. Furthermore it is now recognized that resistance to left ventricular ejection cannot be described fully by aortic valve function alone but must include consideration of aortic and peripheral vascular compliance[185][186][119]. The systolic load on the left ventricle, the total LV outflow impedance (Z_{VA}), may be high even in the presence of relatively moderate

stenosis at valve level[185]. Currently no measure exists that integrates valvular and vascular afterload with dynamic left ventricular function.

The aim of the present study was to compare the physiological characteristics of patients with moderate to severe AS who volunteer symptoms, with those of patients with revealed symptoms during exercise or are truly asymptomatic even during exercise. Specifically, we sought to examine how flow, transaortic gradient and vascular physiology interact during exercise and to determine whether a physiological parameter that integrates these components might predict exercise capacity and the need for aortic valve surgery.

5.3 Methods

A detailed description of the resting echocardiography, stress echocardiography and exercise tolerance test protocols can be found in the methods chapter (chapter 2). Only the patient selection/allocation and details of statistical analysis is described below.

5.3.1 Patients

We prospectively studied consecutive patients with aortic stenosis referred to a specialist valve clinic at Guys and St Thomas' Hospital. Inclusion criteria were an effective orifice area (by the continuity equation) $<1.5cm^2$ and left ventricular ejection fraction (LVEF) $\geq$ 50%. Patients were excluded from the study if they reported recent syncope, had more than mild mitral valve disease or had any significant co-morbidity that might reduce exercise ability (e.g. peripheral vascular disease and pulmonary disease).

All patients underwent detailed evaluation of symptoms, clinical examination, 12-lead electrocardiogram, B-type natriuretic peptide measurement at rest (measured using the point-of-care Triage BNP assay (Biosite diagnostics, California, USA)), transthoracic echocardiography, modified-Bruce protocol treadmill exercise tolerance test and bicycle stress echocardiography. Written informed consent was obtained from all patients and the study was approved by the institutional ethics committee (NHS REC reference: 12/LO/1787).

Based on the clinical history, patients were initially categorized into two groups: those with volunteered symptoms and those who denied symptoms. Following exercise treadmill testing, those patients who denied symptoms were further sub-divided into two further categories: truly asymptomatic and those with revealed symptoms on exercise. All patients with symptoms (volunteered and revealed) were referred for aortic valve replacement.

In order to evaluate the parameters that determine exercise capacity and the presence of revealed symptoms on exercise, those patients with spontaneously volunteered symptoms were excluded from further analysis. A study flow chart is shown in figure 5.1.

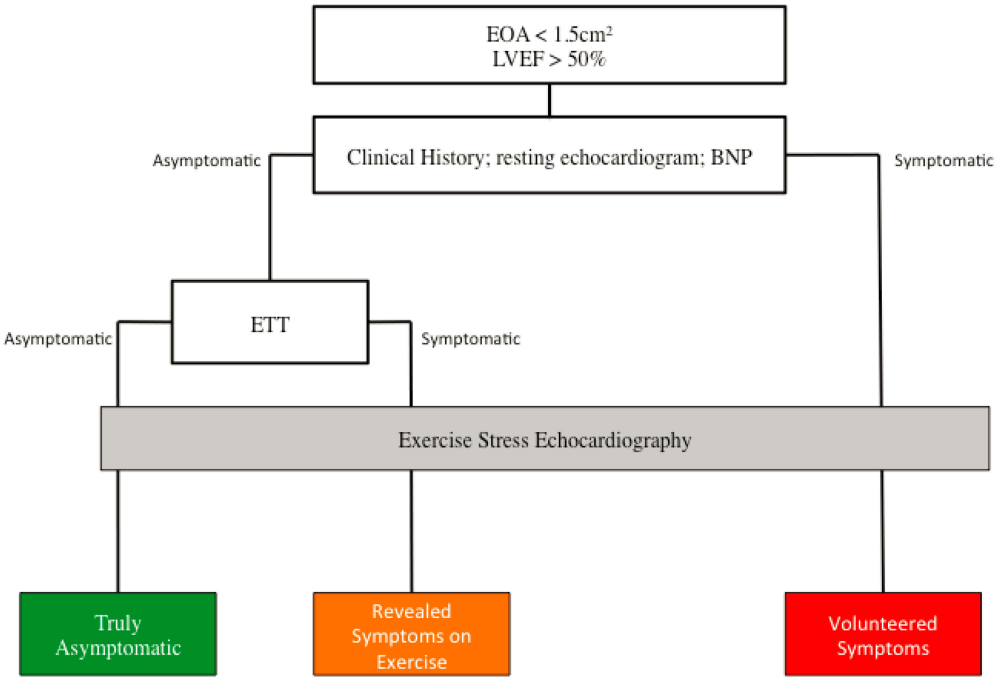

Figure 5.1: Study Flow chart

5.3.2 Statistical Analysis

All continuous variables included in the analysis are presented as mean ± SD. Variables with non-normal distributions are presented as median with interquartile range. Comparison of continuous variables was performed using the independent sample t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed data. The difference in the proportions of nominal variables was assessed using chi-squared or Fisher's exact test were appropriate.

The influence of variables on exercise capacity (EC) was studied on univariate analysis. The strongest univariate predictors (up to a maximum of 5 to avoid over-fitting) were subsequently included into a multiple linear regression model (Backward method). To avoid colinearity among a subset of several variables measuring the same phenomenon (e.g. peak and mean gradients), we entered in the multivariate models the variable that had the strongest association with the endpoint on univariate analysis.

Influence of variables on the referral for surgery was studied on univariate analysis (point biserial correlation). Areas under curve (AUC) for sensitivity and specificity were calculated using receiver-operating characteristic (ROC) analysis to assess prognostic accuracy of different parameters. Likelihood ratios were used to determine optimal cut-off values for predicting symptoms.

For all analyses, a p-value of 0.05 was considered significant. All p-values were two-sided. Statistical analyses were performed using the SPSS 21 and Prism GraphPad 6.0.

5.4 Results

5.4.1 Patient Characteristics

48 patients aged 68.8 ± 10.5years were recruited, of whom 77% were male. 52% had a history of hypertension and 42% had hypercholesterolaemia. At rest the mean EOA was 0.94 ± 0.29 cm^2 and the mean AVG was 33.6 ± 11.3 mmHg. During maximal bicycle exercise the EOA increased to 1.03 ± 0.37cm^2 and the mean AVG increased to 53.1 ± 19.2mmHg.

Table 5.1 shows details of patient demographics, echocardiographic and exercise tolerance test parameters, categorised by symptoms volunteered on initial clinical history.

	History		
	Denies Symptoms	Volunteered Symptoms	p-value
Number of patients	36	12	
Age(yrs)	67 ± 11	75 ± 7	0.021
BNP(pg/ml)	75 ± 95	197 ± 178	0.004
	Exercise Tolerance Test		
EC(s)	729 ± 228	436 ± 323	0.001
HR_{REST} (bpm)	74 ± 13	74 ± 13	0.98
HR_{PEAK} treadmill (bpm)	139 ± 23	123 ± 21	0.05
	Resting Echocardiography		
$meanAVG_{REST}$ (mmHg)	32 ± 11	40 ± 11	0.029
$peakAVG_{REST}$ (mmHg)	52 ± 17	64 ± 15	0.046
EOA_{REST} (cm^2)	0.98 ± 0.31	0.87 ± 0.13	0.25
CO_{REST} (l/min)	5.1 ± 1.6	5.4 ± 1.0	0.61
Lateral S' (ms-1)	0.087 ± 0.022	0.072 ± 0.019	0.045
E/E'	8.3 ± 1.9	16.9 ± 6.6	0.003
	Exercise Echocardiography		
HR_{PEAK} (bpm)	118 ± 21	108 ± 15	0.13
$meanAVG_{EX}$ (mmHg)	51 ± 17	60 ± 23	0.17
$peakAVG_{EX}$ (mmHg)	82 ± 24	97 ± 35	0.1
EOA_{EX} (cm2)	1.11 ± 0.42	0.85 ± 0.21	0.044
CO_{EX} (l/min)	10.1 ± 3.2	8.1 ± 1.5	0.048
COR	100 ± 47	54 ± 35	0.003
ΔmeanAVG (mmHg)	20 ± 12	20 ± 14	0.86

Table 5.1: Demographics, cardiac risk factors, basic echocardiographic parameters, results of the exercise tolerance test and exercise stress echocardiography in recruited patients. Patients are categorised by their clinical history. EC, exercise capacity; BNP, b-type natriuretic peptite; HR, heart rate; meanAVG, mean aortic valve gradient; peakAVG, peak aortic valve gradient; EOA, effective orifice area; lateral S', peak systolic velocity of the lateral mitral valve annulus; E/E', ratio of mitral inflow velocity to velocity of the mitral valve annulus during passive left ventricular filling; COR, cardiac output reserve; ΔmeanAVG, change in mean aortic valve gradient from rest to exercise; Subscript of $_{REST}$ denotes measurements taken at rest; Subscript of $_{EX}$ denotes measurements taken during maximal exercise

Following exercise tolerance testing, patients were divided into three groups: truly asymptomatic, revealed symptoms on exercise and volunteered symptoms. Table 5.2

shows patient demographics, echocardiographic and exercise tolerance test parameters of these three groups.

Two patients developed regional wall motion abnormalities on exercise; both patients were found to have significant coronary artery disease at angiography. Two further patients referred for surgery had flow limiting coronary artery on coronary angiography. Of these four patients demonstrated to have coronary artery disease three went on to have AVR plus coronary artery bypass grafting and one was treated with percutaneous coronary revascularization. A sub-group analysis excluding these patients with coronary artery disease yields the same overall results.

	Symptom Status after Exercise Test				
	Truly Asymptomatic	Revealed on Exercise	Volunteered Symptoms	p-value (asymptomatic vs. revealed)	p-value (revealed vs. volunteered)
Number of patients	23	13	12		
Age(yrs)	63 ± 10	73 ± 10	75 ± 7	0.01	0.62
BNP(pg/ml)	46 ± 51	135 ± 134	197 ± 178	0.01	0.36
	Exercise Tolerance Test				
EC(s)	831 ± 138	548 ± 246	436 ± 323	<0.001	0.34
HR_{REST} (bpm)	74 ± 12	73 ± 16	74 ± 13	0.77	0.87
HR_{PEAK} treadmill (bpm)	148 ± 14	123 ± 28	123 ± 21	0.001	1
	Resting Echocardiography				
$meanAVG_{REST}$ (mmHg)	27 ± 9	39 ± 9	40 ± 11	0.001	0.91
$peakAVG_{REST}$ (mmHg)	46 ± 15	64 ± 16	64 ± 15	0.001	0.97
EOA_{REST} (cm^2)	1.07 ± 0.32	0.82 ± 0.24	0.86 ± 0.13	0.02	0.57
CO_{REST} (l/min)	5.1 ± 1.6	5.2 ± 1.6	5.4 ± 1.0	0.92	0.69
Lateral S' (ms-1)	0.090 ± 0.019	0.081 ± 0.026	0.072 ± 0.019	0.22	0.35
E/E'	8.2 ± 2.7	8.3 ± 0.4	16.9 ± 6.6	0.38	0.14
	Exercise Echocardiography				
HR_{PEAK} (bpm)	124 ± 17	107 ± 24	108 ± 16	0.02	0.98
$meanAVG_{EX}$ (mmHg)	47 ± 16	59 ± 18	60 ± 23	0.04	0.89
$peakAVG_{EX}$ (mmHg)	77 ± 23	91 ± 24	97 ± 35	0.11	0.59
EOA_{EX} (cm2)	1.28 ± 0.39	0.81 ± 0.27	0.85 ± 0.21	0.001	0.68
$CO_{EX\ (l/min)}$	11.3 ± 3.1	7.9 ± 2.4	8.1 ± 1.5	0.001	0.79
COR	126 ± 35	55 ± 27	54 ± 35	<0.001	0.95
ΔmeanAVG (mmHg)	20 ± 10	20 ± 14	20 ± 4	0.99	0.89

Table 5.2: Demographics, cardiac risk factors, basic echocardiographic parameters, results of the exercise tolerance test and exercise stress echocardiography in recruited patients. Patients are categorized into three groups, truly asymptomatic, revealed symptoms and volunteered symptoms. EC, exercise capacity; BNP, b-type natriuretic peptite; HR, heart rate; meanAVG, mean aortic valve gradient; peakAVG, peak aortic valve gradient; EOA, effective orifice area; lateral S', peak systolic velocity of the lateral mitral valve annulus; E/E', ratio of mitral inflow velocity to velocity of the mitral valve annulus during passive left ventricular filling; COR, cardiac output reserve; ΔmeanAVG, change in mean aortic valve gradient from rest to exercise; Subscript of $_{REST}$ denotes measurements taken at rest; Subscript of $_{EX}$ denotes measurements taken during maximal exercise

5.4.2 Exercise Treadmill Testing

The EC was 832 ± 138s in the truly asymptomatic patients and 548 ± 246 in patients with revealed symptoms ($p < 0.001$). The maximum heart rate in the truly asymptomatic and those with revealed symptoms was 148 ± 14 and 123 ± 28 ($p = 0.001$) respectively.

5.4.3 Response to Bicycle Exercise

The following parameters increased significantly from rest to maximal bicycle exercise, in truly asymptomatic patients and those with revealed symptoms: heart rate, mean aortic valve gradient, peak aortic valve gradient, cardiac output ($p < 0.001$ for these parameters in both groups). In truly asymptomatic patients, the effective orifice area increased in response to exercise ($p < 0.001$) but did not change in patients with revealed symptoms ($p = 0.73$). The LV outflow impedence (Z_{VA}) did not change in response to exercise in truly asymptomatic patients ($p = 0.27$) but increased in patients with revealed symptoms ($p = 0.003$). There was a significant rise in stroke volume and energy loss index in truly asymptomatic patients ($p < 0.001$ and $p = 0.009$ respectively) but no change in those with revealed symptoms ($p =0.42$ and $p = 0.63$ respectively).

Compared to resting measurements, the percentage increase in cardiac output at each workload was significantly greater in truly asymptomatic patients compared to patients with revealed symptoms (Figure 5.2).

EOA was lower and gradients across the valve were higher, at rest and at each level of workload, in patients with revealed symptoms than truly asymptomatic patients, however there was no difference in the percentage change from rest.

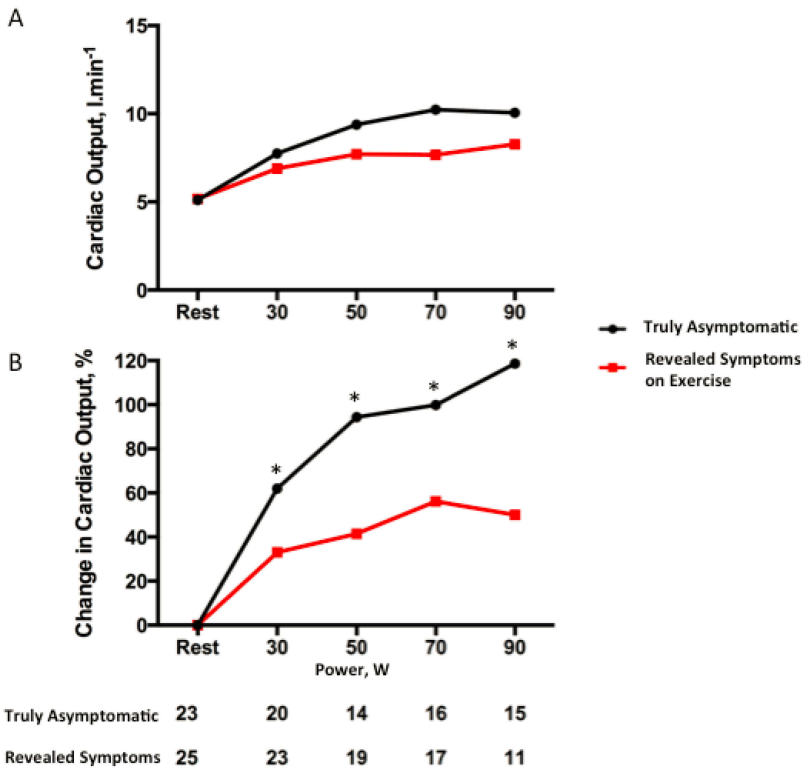

*Figure 5.2: Truly Asymptomatic Patients are displayed in red and those with revealed symptoms in black. *denotes a significant difference between truly asymptomatic and patients with revealed symptoms (α = 0.05). A: Cardiac output at each workload. B: Relative change in cardiac output at each workload. The number of patients in each group at each workload is shown below the y-axis in B.*

5.4.4 Determinants of Exercise Capacity (EC)

The COR correlated most strongly with EC followed by age, E/E', SVR and BNP (table 5.3). Classical resting measures of AS severity did not correlate with EC. By multiple linear regression, COR and age were the only independent predictors of exercise capacity (table 5.3).

Parameter	Univariate r	p-value	Multivariate Standardised β	p-value
COR	0.67	<0.001	0.48	0.001
Age	0.62	<0.001	0.41	0.005
LA area	0.56	<0.001	-	-
SVR	0.53	<0.001	-	-
BNP	0.42	0.02	-	-
ΔmeanAVG	0.39	0.02	-	-
HRR	0.39	0.02	-	-

Table 5.3: Univariate and multivariate predictors of exercise capacity. COR, cardiac output reserve; LA area, left atrial area; SVR, stroke volume reserve; BNP, b-type natriuretic peptide; ΔmeanAVG, change in mean aortic valve gradient from rest to maximal exercise; HRR, heart rate reserve.

5.4.5 Revealed Symptoms on Exercise

Receiver operating characteristic (ROC) curves for those independent variables with the largest AUC is shown in figure 5.3.

A COR of 77% was determined as the optimal cut-off value for maximizing the sensitivity and specificity to predict revealed symptoms. Using this cut-off value COR is 92% sensitive and 100% specific for identifying revealed symptoms and hence the need for surgery in patients who denied symptoms. Associated positive predictive and negative predictive values are 100% and 96% respectively.

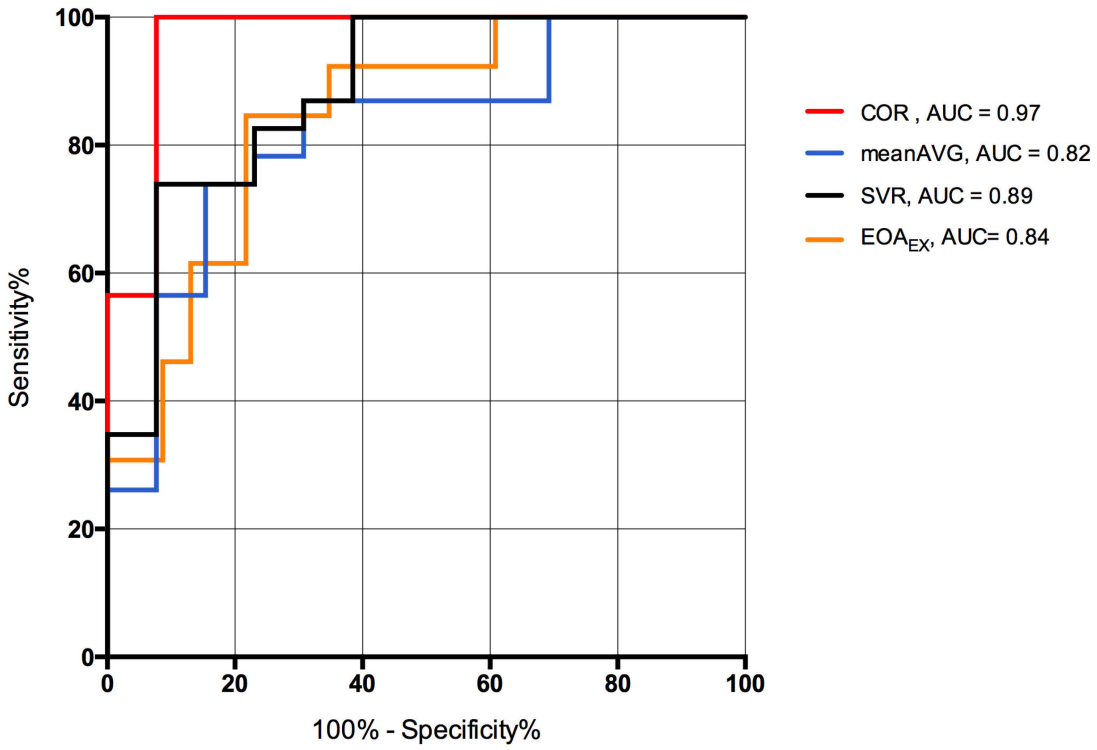

Figure 5.3: Receiver Operator Characteristics Curves (ROC) for the predictors of referral for aortic valve surgery. The four indices with the largest area under the curve (AUC) are shown. COR, cardiac output reserve; SVR, stroke volume reserve; EOA_{EX}, effective orifice area during maximal exercise; meanAVG, mean aortic valve gradient under resting conditions.

5.5 Discussion

5.5.1 Main Findings

The main findings of this study are:

- Treadmill exercise can be used to further evaluate patients with aortic stenosis who deny symptoms. Patients with revealed symptoms on exercise and those who volunteer symptoms during history-taking are physiologically similar
- COR is an objective measure that integrates the physiological contributions of valve, ventricle, systemic circulation and chronotropic competence. It is an independent predictor of exercise capacity in patients who deny clinical symptoms and correlates strongly with the likelihood of these patients developing symptoms during exercise

5.5.2 Clinical history and exercise testing AS

Symptoms may develop insidiously in AS and may not be obvious either to the patient or cardiologist. This makes the clinical history unreliable. It is well established that approximately one third of patients who deny symptoms during the clinical history are deemed symptomatic after exercise testing[184][181][112][111][183].

The results of this study are consistent with these previous reports, with 36% of those who denied symptoms on the clinical history becoming symptomatic during exercise.

Those patients with revealed symptoms were physiological inseparable to patients who spontaneously volunteered symptoms, both at rest and during exercise. This is a finding that has not previously been demonstrated, as previous groups have not exercised patients with symptoms. On the other hand, using traditional indices, truly asymptomatic patients had less severe AS, than patients with volunteered symptoms.

Despite the important role of exercise testing in AS [111][187][113], it is not without limitations. Key to the interpretation of an ETT is the subjective identification of symptoms, which is dependent on the operator/physician experience, as well as their interaction with the individual patient during the test. In addition the sensation of symptoms by the patient is highly variable and influenced by personality and mood as well as cultural differences in reporting these symptoms[141]. Age has been shown to be the strongest independent predictor of exercise capacity in AS and therefore acts as a powerful confounder when interpreting ETTs[120]. Hence there is a need for a more objective way of interpreting these tests, rather than the relying purely on clinical judgement, particularly outside specialist centres.

The measurement of COR may represent a step towards reducing the subjectivity of interpreting individual performance on exercise tests. Furthermore, measuring COR during cardiopulmonary exercise testing may negate the need for bicycle stress echocardiography, which would not be feasible in centres without this expertise.

5.5.3 Utility of exercise echocardiography in AS

The classical measures of AS severity, aortic valve gradients and effective orifice area, were significantly different between truly asymptomatic patients and patients with revealed symptoms at each level of exercise intensity. However, the percentage change from resting values in these measurements was not significantly different between groups. This finding signifies that using these measures during exercise does not aid further differentiation of patients.

In our study cohort only the integrative measures, including SVR and COR, could be used to further distinguish the two groups. This difference was apparent at all levels of exercise intensity and hence COR is not an artifact of shorter exercise times. This blunted rise in SV and CO has been shown previously in AS[179].

In this study we found no difference in the change in mean AVG on exercise, a finding which appears incongruent with previous publications showing that patients with positive exercise tests have poorly compliant aortic valves [117][118] and that rise in mean AVG during exercise by more than 18-20mmHg is associated with worse long-term outcomes[180][183]. However the latter would only be expected to occur in the presence of preserved contractile reserve. It is possible some of our enrolled patients had impaired contractile reserve that prevented large increases in aortic valve gradients during exercise.

5.5.4 Cardiac Output Reserve

The rationale for using COR, which is dimensionless, rather than peak CO or absolute change in CO is that, the oxygen demands per gram of tissue will vary from patient to

patient (and hence CO requirements will vary). Using COR allows each individual patient to act as his or her own control. It is analogous to the coronary flow reserve used in coronary physiology[52].

In cardiopulmonary exercise testing, maximal oxygen consumption (VO_2max) is regarded as the metric that defines cardiopulmonary limits[141]. Patients known to have pulmonary disease were excluded from the study and our cohort are assumed to have normal gas exchange; therefore cardiac function and hence cardiac output would be expected to represent the limiting factor in EC. COR integrates the interactions of aortic valve, left ventricle, systemic circulation and also chronotropic response, making it a physiologically appealing index for evaluation of AS.

The importance of this dynamic coupling has been recognized previously. In a prospective follow-up study of 163 asymptomatic patients with moderate-severe AS, four independent predictors of adverse events were identified using a cox-regression model: peak AVG; left ventricular systolic (LV) longitudinal deformation, valvulo-arterial impedance and indexed left atrial area[102]. Although these individual factors are shown to influence outcomes, these variables are not independent of one another and therefore interpreting each in isolation introduces error. Each of these factors will contribute to a reduction in COR and this is where the potential strength of COR lies, as an integrated index.

Using the SVR rather than COR is an alternative approach, as this may be considered a purer reflection of the interaction between valve and ventricle. While the SVR did correlate with both EC univariate analysis ($r = 0.53$, $p < 0.0001$), it was not found to be an independent predictor in the regression analysis. SVR was also a strong

predictor of surgery on the ROC analysis but had a smaller area under the curve than COR. The reason for this shortcoming is related to the chronotropic response to exercise in this study.

Heart rate reserve was significantly less in those with revealed symptoms, which goes against expectations. In response to the blunted rise in stroke volume seen in this group of patients, one would expect the heart rate to increase by a greater proportion to meet the demand for an increased cardiac output. This observation may be indicative of chronotropic incompetence. To our knowledge this is the first study to highlight this association. Chronotropic incompetence has been shown to predict clinical outcome in patients with coronary artery disease, congenital heart disease and in healthy populations [188][189][190]; its importance in AS requires further exploration.

5.5.5 Limitations and future research

The main limitations of our study are the relatively small sample size and the use of revealed as one of the dependent endpoints. Even in experienced hands the identification of symptoms is subjective and the decision may vary between physicians and institutions. While more objective clinical endpoints such as death or major adverse cardiac events would be theoretically preferable, we were unable to consider such a study design for ethical as well as resource considerations.

Further studies should focus on truly asymptomatic patients to determine whether COR can improve the risk stratification in this cohort.

Four of the enrolled patients (9%) were on beta-blocker therapy. It is possible that heart rate augmentation on exercise was limited in these patients.

We did not measure left ventricular ejection fraction or pulmonary artery systolic pressure during maximal exercise as we decided to focus on achieving the best quality LVOT and AV Doppler traces. The inclusion of these parameters would strengthen studies.

5.5.6 Conclusions

History taking in AS is an unreliable way of identifying symptoms. Exercise testing can be used to risk stratify seemingly asymptomatic patients with moderate to severe AS. The current study suggests that the novel index of COR may be a useful adjunct for clinicians in adjudicating the presence of exercise-induced symptoms and the need for AVR. The utility of COR in determining the need for surgery and the incidence of major adverse events will need to be assessed in larger prospective observational studies of patients without declared symptoms.

Chapter 6: Synthesis

6.1 Origins of the thesis

Primarily, this thesis is about the dynamic interaction of the aortic valve, left ventricle and coronary circulation at rest and during exercise. It is easy to think of each of these structures in isolation, however, this simplistic view is not adequate to fully understand the pathophysiology of disease or further our clinical risk stratification models. Any structural change in the aortic valve will change the left ventricular afterload and hence the contractile state of the ventricle; both this altered contractile state and pressure drop across the aortic valve alter the coronary flow profile. Furthermore, alterations in the structure and function of the microvasculature will modulate these interactions. Changes to coronary flow in turn may lead to further change in ventricular mechanics and remodeling.

I have attempted to unravel these complex dynamic interactions through the measurement of pressure and flow in the coronary circulation as well as across the aortic valve. By looking at changes in both pressure and flow simultaneously under different conditions, it has been possible to make inferences on the coupling mechanisms between valve and ventricle on the one hand, as well as valve, ventricle and coronary circulation.

The idea that developed into this body of work arose from two related, but independent observations: Firstly, we have known for over 30 years that coronary flow reserve was reduced in patients with aortic stenosis and normal coronary arteries, but the mechanism was poorly understood; Secondly, the poor correlation between echocardiographic markers of aortic stenosis severity and symptoms of aortic stenosis.

The study described in chapter 3 aimed to decipher the mechanisms of reduced CFR in patients with unobstructed epicardial coronary arteries and aortic stenosis. We believe that WIA is an ideal tool to disentangle the complex interactions between contracting myocardium, valve and the coronary circulation.

Sunsequently we sought to understand the effects of microvascular function on the dynamic changes in coronary flow, independent of aortic valve disease. As with Aortic Stenosis, the other group of patients who have symptoms of inducible ischaemia even in the absence of epicardial coronary disease are patients with microvascular dysfunction. In recruiting the control cohort for the aortic stenosis coronary physiology study, we observed many more patients than anticipated with visually "normal" epicardial arteries (determined by FFR) but abnormal CFR. This pathophysiological state drew many parallels to aortic stenosis in how the coronary circulation and ventricle interacted at rest but importantly how this dynamic interaction changes during exercise or with the induction of hyperemia. Naturally we wanted to quantify this discrepancy and apply similar techniques that had proven successful in aortic stenosis to patients with microvascular disease.

The study described in chapter 5 was designed to explore the second of these observations. Ample evidence exists that the development of symptoms in aortic stenosis is not simply related to the degree of valve stenosis; it is how the ventricle adapts to this increase in afterload, the mechanical properties of the valve (compliance) and the afterload imposed by the systemic arterial tree.

6.2 Aims of the thesis

Given the complexity of the methods employed in chapter 3, the study was never expected to lead to new indices of disease severity, rather this was a study directed to understanding the pathophysiology of reduced CFR in aortic stenosis. We wanted to determine whether the mechanism was driven predominantly by changes in vascular microvascular resistance associated with ventricular remodeling or related to changes in compressive microvascular resistance, through cardiac-coronary coupling.

Patients with coronary microvascular disease, by definition, have abnormal responses to different stressor agents (e.g. acetylcholine, adenosine). The presence of microvascular disease is associated with poor long-term outcomes. The aim of the study described in chapter 4 was to use different forms of stress, exercise and adenosine, to determine the possible underlying pathophysiology of coronary microvascular disease. Also to use simultaneous measures of pressure and flow to appreciate how abnormalities of microvascular resistance modulate cardiac-coronary coupling and coronary perfusion efficiency.

Following directly from the recognition of the limitations of current indices and models of risk stratification in AS, one aim of the thesis was to develop an index that would integrate the severity of valve stenosis, left ventricular function and the afterload imposed by the systemic circulation. We hoped that this index could be shown to predict exercise capacity and presence of revealed symptoms on exercise.

6.3 Summary of Main Findings

6.3.1 Coronary Physiology of Aortic Stenosis During Stress: An Imbalance of Forces

We found that patients with severe aortic stenosis had normal values of minimal microvascular resistance and diastolic microvascular resistance during hyperemia. This provides evidence that the vascular component of microvascular resistance is intact in aortic stenosis. Therefore abnormalities of cardiac-coronary coupling appear to be the dominant factor in the failure of patients with aortic stenosis to adequately augment flow in proportion to increases in cardiac work. The inability to adequately augment coronary flow is secondary to a pathophysiological imbalance of forces accelerating and decelerating coronary flow in AS during stress. While the efficiency of the healthy heart improves during exercise and hyperemia, manifested by an increase in the relative contribution of waves that accelerate flow, the reverse is observed in AS, where decelerating waves become more important with stress. Hence coronary perfusion efficiency is reduced. It is an augmented rise in the backward compression wave (BCW) and an attenuated rise in the forward compression wave (FCW) that causes this impaired efficiency.

6.3.2 Coronary Microvascular Disease: Impaired Flow and Impaired Efficiency

In this chapter, we found that patients with MVD, at rest, had elevated coronary flow and lower microvascular resistance, this novel finding is likely to be indicative of dysfunctional resting autoregulatory state.

In response to stress, this cohort has a smaller relative reduction in microvascular resistance and hence attenuated flow augmentation. Therefore the reduction in CFR in MVD is multifactorial secondary to resting vasodilation and impaired minimal microvascular resistance.

This dysfunctional coronary microcirculation not only reduces maximal coronary flow, but also impairs coronary perfusion efficiency. These processes render the myocardium more susceptible to ischemia.

6.3.3 Cardiac Output Reserve – An Integrated Measure of Afterload and Left Ventricular Function in Aortic Valve Stenosis

We have shown that exercise testing is a powerful tool to risk-stratify asymptomatic patients with Aortic Stenosis and that the group with revealed symptoms on exercise are physiologically similar to those who volunteer symptoms during history-taking. COR is an objective measure that integrates the physiological contributions of valve, ventricle, systemic circulation and chronotropic competence. It is an independent predictor of exercise capacity in patients who deny clinical symptoms and is the strongest predictor of the likelihood of these patients developing symptoms during exercise.

This is a proof of concept study and it remains to be seen how this index is accepted in the cardiology community and whether the results can be repeated in other institutions. Pending further validation studies and clinical outcome trials, it is conceivable that Cardiac Output Reserve may find its way into clinical practice and help clinicians risk stratify patients with aortic stenosis, ensuring patients are referred for intervention at the appropriate time.

6.4 Important considerations

6.4.1 What is a wave?

One's concept and understanding of what constitutes a wave varies, however remains pivotal to the understanding and application of wave intensity analysis and therefore warrants careful exploration. Physiologists trained in the classical methods of hemodynamics (impedance methods) will think of waves as sinusoidal waveforms. In impedance analysis, a waveform (such as a pressure waveform) can be decomposed into its fundamental and higher harmonic frequencies. Hence impedance analysis is a frequency domain method of studying hemodynamics.

In many ways wave intensity analysis is more intuitive and simpler to understand, as it is a time domain analysis. In WIA, waveforms are divided into many discrete time intervals of equal duration (sampling period). The waveform is then formed from the

successive changes in pressure (or flow velocity) in each sampling interval (figure 6.1). Each of these successive changes in pressure is termed a wavefront.

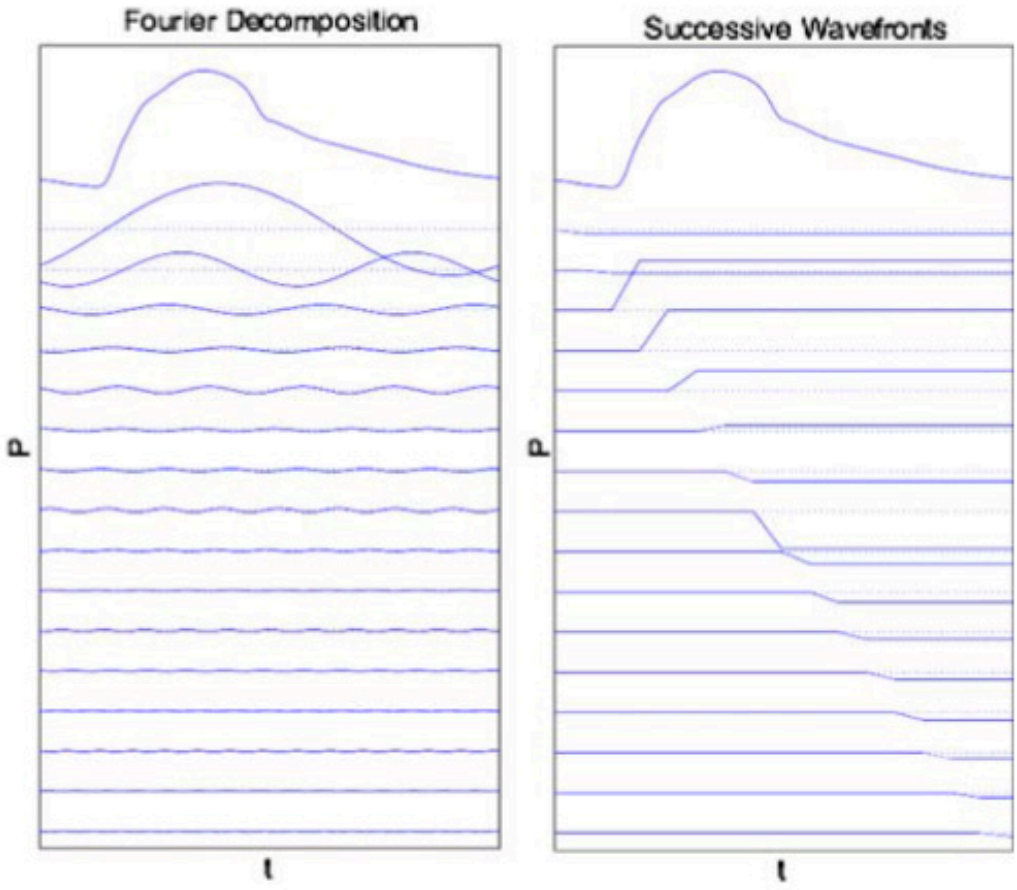

Figure 6.1: Reproduced from [58]. The decomposition of the pressure waveform measured in a human aorta into sinusoidal wavetrains (left) and successive wave- fronts (right). In each figure, the measured pressure is shown at the top. In the Fourier representation, the fundamental and first 15 harmonics are shown. In the right hand figure the successive wavefronts are obtained by dividing the cardiac period into sixteen equal time intervals and plotting the change in pressure during each interval.

Net wave intensity is defined as the product of the change in pressure and change in velocity in each time interval (the product of the pressure and velocity wavefronts in each sampling interval). If the net wave intensity is positive then the forward waves

are dominant in that window of the cardiac cycle (originate in the aorta) and if the net wave intensity is negative, then the backward waves are dominant (originate from the microcirculation).

The fundamental question remains: What does this mean? And how does this forward our understanding of the coronary circulation?

A clue to the meaning of a wave (in WIA) lies in its units. In WIA, a wave has the units power per unit area (Wm^{-2}). This equates to the energy flux per unit area that the wave carries as it propagates along the vessel. Therefore, through separation of the net wave intensity into its forward and backward components, it is possible to quantify the total energy flux propagating along the artery at any one point. Although WIA has traditionally focused on the contributions of forward and backward components, in this thesis, we have placed emphasis on the relative balance of accelerating and decelerating waves. An accelerating wave can be thought of as a quantum (or packet) of energy driving flow and a decelerating wave as a quantum of energy impeding flow, the presence of two or more waves at any one point combine to either, cancel one another out, or summate.

By calculating the percentage contribution to total wave intensity of accelerating and decelerating waves over the cardiac cycle, a quantitative measure of the relative balance of the energy that drives and impedes coronary flow results. A greater proportion of accelerating waves implies that a greater the proportion of energy produced by the (contracting and relaxing) myocardium drives flow. As the balance shifts to a greater percentage of decelerating energy, more of this cardiac energy is impeding flow. Hence we have a measure of coronary perfusion efficiency.

We must issue caution to this proposed concept of coronary perfusion efficiency. Although the wave intensity represents an energy flux within the artery of interest,

this energy flux does not account for all of the energy carried in the wave and is less than the total kinetic and potential energy the wave possesses[58].

6.4.2 Wave Intensity and the Inference of Left Ventricular Dynamics

We have seen in chapters 4 and 5 that the magnitude of wave intensity is intimately related to the microvascular tone. The lower the MR the greater the value of the wave intensity. Furthermore, the absolute magnitude of wave intensity is much greater during exercise, a physiological state that we know leads to increased myocardial contractility and altered filling conditions. We can therefore infer that wave intensity is also determined by the prevailing hemodynamics conditions and left ventricular contractility. Unravelling the relative contributions of each parameter to the total wave intensity is extremely complex. Although WIA provides a window into these ventricular mechanics, particularly during minimal microvascular resistance, I believe much more work is required to fully understand these interactions. Key to extrication of this puzzle will be the simultaneous study of coronary physiology and left ventricular mechanics simultaneously, whilst controlling hemodynamic conditions. The study of left ventricular mechanics with pressure-volume loops would provide much needed insight. To allow control of hemodynamic variables, an animal model would be an appropriate starting point.

6.4.3 Clinical Applications of Wave Intensity Analysis

Coronary wave intensity analysis has, to date, been used to study several different disease processes including left ventricular hypertrophy, aortic stenosis, the response to pacing and the warm-up angina phenomenon[155][144][150][149]. Each of these studies has contributed to our understanding of physiology but all are without direct clinical application. So far only one study has explored a clinical application of a wave intensity derived index, where the dominant backward compression wave was shown to be predictive of myocardial viability following non-ST elevation myocardial infarction[156]. The instantaneous free wave ratio used WIA in its original derivation but in fact does not require WIA for its application.

WIA provides unique mechanistic insights into the pathophysiology of disease process, however, I suspect that it may be some time before we have clinical applications that could guide or change management. The reason for this is not fallibility of the theory but rather the practicalities of WIA. There are several hurdles to overcome before this technique becomes accessible to more than just a handful of institutions across the world. Firstly WIA requires the simultaneous measurement of pressure and flow (flow velocity). Unfortunately obtaining good quality and consistent Doppler flow velocity envelopes requires operator experience and skill. Secondly the wires used to acquire these signals are not particularly durable and decay in the quality of flow signal is often seen throughout these complex procedures. Third, by nature of the underlying mathematics of WIA, any error or inappropriate gain in either the pressure or flow signals will be amplified. As the change in pressure is multiplied by the change in flow for each sampling period, errors are multiplied by one another. With poor quality waveforms, true physiological signal

becomes very difficult to differentiate from noise, how one deals with noise is also a complex problem. The introduction of the Savitzky-Golay smoothing filters were a major advance in how physiological signals could be handled, but the level of filtering and precise algorithms used by different groups is rarely reported. How one calculates the wavespeed used for the separation of waves into forward and backward components under different conditions is also controversial[157]. Finally it is important to highlight, that as with all models, WIA does not represent an exact description of the physiology of the arterial tree, it relies on several underlying assumptions. In the derivation of WIA, one-dimensional tube laws are applied: the vessels are assumed to be long straight tubes. WIA also assumes the velocity across the cross-section of the vessel to be fixed. Extensions of WIA exist to partly overcome some of these limitations, the best known being the reservoir wave hypothesis, however as with most theories it has strong advocates and adversaries[191][192][193][194]. Although direct real-time clinical application of WIA remains some way off, its power as a research tool in coronary hemodynamics is undoubted.

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